# DESCRIPTION

## THIENOPYRIDINE DERIVATIVES

### Technical Field

The present invention relates to a compound promoting osteogenesis.

### Background Art

It is known that thienopyridine derivatives have IκB kinase complex inhibitory effect (see Patent Document 1). In addition, 3-amino-4-(dimethylamino)thieno[2,3-b]pyridine-2-carboxamide and 3-amino-4-anilinothieno[2,3-b]pyridine-2-carboxamide are known compounds (see Non-Patent Document 1). However, the influence that these compounds give to bone has not been reported.

[Patent Document 1]

WO03/103661

[Non-Patent Document 1]

Pharm. Chem. J. (Engl. Transl.), 26, 870-874 (1992)

### Disclosure of the Invention

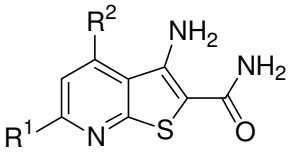
### Problems to be Solved by the invention

The present inventors have conducted intensive studies on compounds that promote osteogenesis, and consequently have found that thienopyridine derivatives have excellent pharmacological effect and thus completed the present invention.

### Means for Solving the Problems

The present invention relates to

(1) a compound having the following general formula (I)

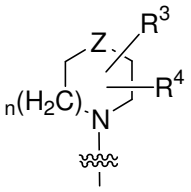



(I)

[wherein

$R^1$ represents a hydrogen atom, the cyclopropyl group or a $C_1$-$C_6$ alkyl group,

$R^2$ represents $R^aS$-, $R^aO$-, $R^aNH$-, $R^a(R^b)N$- or a group




wherein $R^a$ and $R^b$ are the same or different and independently represent a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; or a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms,

$R^3$ and $R^4$ are the same or different and independently represent a hydrogen atom; a group selected from Substituent Group α, Substituent Group β and Substituent Group γ; a $C_1$-$C_6$ alkyl group substituted with one or more groups selected from

Substituent Group γ; or a $C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group γ,

or when $R^3$ and $R^4$ are bonded to adjacent carbon atoms, $R^3$ and $R^4$ together with the carbon atoms to which they are bonded may form a $C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; or a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms,

Z represents a single bond; a double bond; an oxygen atom; a sulfur atom; sulfinyl; sulfonyl; or a group having the formula $R^5N<$;

$R^5$ represents a hydrogen atom; a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_2$-$C_6$ alkenyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heteroaryl group which may be substituted

with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a formyl group; a $C_2$-$C_7$ alkylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a 5- to 7-membered heterocyclylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_7$-$C_{11}$ arylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heteroarylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_1$-$C_6$ alkylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_6$-$C_{10}$ arylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heteroarylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_2$-$C_7$ alkoxycarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_7$-$C_{11}$ aryloxycarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; or one or more groups having the formula $R^c(R^d)N$-CO- (wherein $R^c$ and $R^d$ are the same or different and independently represent a hydrogen atom or a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ), and

n represents an integer of 1 to 4,

Substituent Group α represents the group consisting of a halogen atom; a nitro group; a cyano group; a hydroxy group; a group having the formula $R^6$-CO-, the formula $R^e(R^f)N$-, the formula $R^e(R^f)N$-CO- or the formula $R^e(R^f)N$-$SO_2$- (wherein $R^6$ represents a hydrogen atom, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ halogenated alkyl group, a $C_3$-$C_8$ cycloalkyl group, a hydroxy group, a $C_1$-$C_6$ alkoxy group, a $C_6$-$C_{10}$ aryl group or a $C_6$-$C_{10}$ aryloxy group and $R^e$ and $R^f$ are the same or different and independently represent a hydrogen atom; a $C_1$-$C_6$ alkyl group; a $C_1$-$C_6$ alkoxy group; a $C_6$-$C_{10}$ aryl group; a 5- to 7-membered heteroaryl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a formyl group; a $C_2$-$C_7$ alkylcarbonyl group; a $C_2$-$C_7$ alkoxycarbonyl group; a $C_7$-$C_{11}$ arylcarbonyl group; a 5- to 7-membered heteroarylcarbonyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_1$-$C_6$ alkylsulfonyl group; a $C_6$-$C_{10}$ arylsulfonyl group; or a 5- to 7-membered heteroarylsulfonyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms, or alternatively $R^e$ and $R^f$ together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocylyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms (wherein the heterocylyl group may have 1 or 2 substituent groups selected from a hydroxy group and a methyl group)); a hydroxyimino group; a $C_1$-$C_6$ alkoxyimino group; a $C_1$-$C_6$ alkoxy group; a $C_3$-$C_8$ cycloalkyloxy group; a $C_1$-$C_6$ halogenated alkoxy group; a $C_1$-$C_6$ alkylthio group; a $C_1$-$C_6$ alkylsulfinyl group; and a $C_1$-$C_6$ alkylsulfonyl group,

Substituent Group β represents the group consisting of a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α; and a $C_1$-$C_6$ alkyl group substituted with a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α and a $C_1$-$C_6$ alkyl group and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms, and

Substituent Group γ represents the group consisting of a $C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group α; a $C_1$-$C_6$ alkylthio group substituted with one or more groups selected from Substituent Group α; a $C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β; a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β; a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_3$-$C_8$ cycloalkyloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β; a 5- to 7-membered heterocyclyloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β; a 5- to 7-membered heteroaryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; and a $C_6$-$C_{10}$ aryl - $C_1$-$C_6$ alkoxy group in which the aryl moiety may be substituted with one or more groups selected from Substituent Group α and Substituent Group β] or a pharmacologically acceptable salt thereof.

Preferred examples of the above compound are

(2) compounds in which $R^1$ is a hydrogen atom, a cyclopropyl group or a $C_1$-$C_4$ alkyl group,

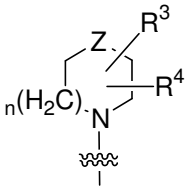
(3) compounds in which $R^1$ is a hydrogen atom, methyl, ethyl, propyl or cyclopropyl,

(4) compounds in which $R^1$ is a hydrogen atom or methyl,

(5) compounds in which $R^2$ is a group $R^a(R^b)N$-, and $R^a$ and $R^b$ are the same or different and independently represent a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ,

(6) compounds in which $R^a$ is a $C_1$-$C_6$ alkyl group which may be substituted with one group selected from Substituent Group α and Substituent Group γ, $R^b$ is a $C_1$-$C_6$ alkyl group, and Substituent Group α is the group consisting of a $C_1$-$C_6$ alkoxy group, and Substituent Group γ is the group consisting of a $C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group α; a $C_6$-$C_{10}$ aryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β; and a 5- to 7-membered heteroaryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms,

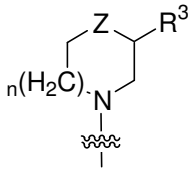
(7) compounds in which $R^2$ is a group




wherein $R^4$ is a hydrogen atom or together with $R^3$ forms a $C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; or a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent

Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms,

(8) compounds in which $R^2$ is a group



wherein Z represents a single bond, an oxygen atom, a sulfur atom or a group having the formula $R^5N<$,

$R^5$ represents a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a formyl group; a $C_2$-$C_7$ alkylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_1$-$C_6$ alkylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_6$-$C_{10}$ arylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heteroarylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_2$-$C_7$ alkoxycarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; or one or more groups having the formula $R^c(R^d)N$-CO-, and n is an integer of 1 to 3,

(9) compounds in which $R^3$ is a $C_1$-$C_6$ alkoxy group; a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α; a $C_1$-$C_6$

alkoxy group substituted with one or more groups selected from Substituent Group α; a $C_6$-$C_{10}$ aryloxy group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a $C_1$-$C_6$ alkyl group substituted with one or more groups selected from Substituent Group γ; or a $C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group γ,

Z is a single bond, and n is 2,

(10) compounds in which $R^3$ is a hydrogen atom, Z is a sulfur atom, and n is 1, and

(11) compounds in which $R^3$ is a hydrogen atom, Z is a group having the formula $R^5N<$, $R^5$ represents a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; or a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms: n is 2

and pharmacologically acceptable salts thereof, and particularly preferred compounds are

(12) any of the compounds selected from the following:

· 3-amino-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]-6-methylthieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{3-[3-(2-hydroxyethoxy)propyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{(3S)-[(2-methoxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{(3S)-3-[(3-methoxypropoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(3-{[2-(dimethylamino)-2-oxoethoxy]methyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(3-{3-[2-(dimethylamino)-2-oxoethoxy]propyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 4-[4-(4-acetylphenyl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-[4-(4-propionylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(dimethylamino)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 4-[4-(5-acetylpyridin-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepan-1-yl)-6-methylthieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(2-methoxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[2-(dimethylamino)-2-oxoethyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[3-(dimethylamino)-3-oxopropyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(azetidin-1-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[2-(dimethylamino)ethyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[3-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(3-hydroxypropyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(1-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(2-oxopropyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(N-hydroxyethaneimidoyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-[4-(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-[4-(1,3-benzoxazol-6-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-[4-(4-hydroxyimino-3,4-dihydro-2H-chromen-7-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide,

· 4-[4-(4-acetyl-1,3-thiazol-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide,

· 4-[4-(5-acetylthiophen-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide, and

· 3-amino-4-(4-{4-[(dimethylamino)carbonyl]-1,3-thiazol-2-yl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide or pharmacologically acceptable salts thereof.

The present invention further relates to

(13) a pharmaceutical composition which comprises a compound selected from any one of the above (1) to (12) or a pharmacologically acceptable salt thereof as an active ingredient {particularly a pharmaceutical composition for prevention or treatment of osteopathy [for example, osteoporosis (for example, postmenopausal osteoporosis, senile osteoporosis or secondary osteoporosis caused by the use of steroids or immunosuppressants), osteopenia or bone destruction associated with rheumatoid arthritis, Paget's disease of bone, bone fracture or dysostosis due to dwarfism] or osteoarthritis},

(14) use of a compound selected from any one of the above (1) to (12) or a pharmacologically acceptable salt thereof as an active ingredient for preparing a pharmaceutical composition {particularly a pharmaceutical composition for prevention or treatment of osteopathy [for example, osteoporosis (for example, postmenopausal osteoporosis, senile osteoporosis or secondary osteoporosis caused by the use of steroids or immunosuppressants, osteopenia or bone destruction associated with rheumatoid arthritis, Paget's disease of bone, bone fracture or dysostosis due to dwarfism] or osteoarthritis},

(15) a method for promoting osteogenesis, suppressing bone resorption and/or improving bone density comprising administering an effective amount of a compound selected from any one of the above (1) to (12) or a pharmacologically acceptable salt thereof to a mammal (for example, a human, horse, cow or pig, preferably a human) or a bird (preferably a chicken, more preferably a female

chicken) {preferably a method for of prevention or treatment of osteopathy [for example, osteoporosis (for example, postmenopausal osteoporosis, senile osteoporosis or secondary osteoporosis caused by the use of steroids or immunosuppressants, osteopenia or bone destruction associated with rheumatoid arthritis, Paget's disease of bone, bone fracture or dysostosis due to dwarfism] or osteoarthritis}.

In the above general formula (I), the "$C_1$-$C_6$ alkyl group" in the definitions of $R^1$, $R^6$, $R^e$ and $R^f$; the $C_1$-$C_6$ alkyl group of "$C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ" in the definitions of $R^a$, $R^b$, $R^5$, $R^c$ and $R^d$; the $C_1$-$C_6$ alkyl group of "$C_1$-$C_6$ alkyl group substituted with one or more groups selected from Substituent Group γ" in the definitions of $R^3$ and $R^4$; the alkyl moiety of "$C_2$-$C_7$ alkylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ" and "$C_1$-$C_6$ alkylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ" in the definition of $R^5$; the alkyl moiety of "$C_2$-$C_7$ alkylcarbonyl group" and "$C_1$-$C_6$ alkylsulfonyl group" in the definition of $R^e$ and $R^f$; the alkyl moiety of "$C_1$-$C_6$ alkylthio group", "$C_1$-$C_6$ alkylsulfinyl group" and "$C_1$-$C_6$ alkylsulfonyl group in the definition of Substituent Group α; the $C_1$-$C_6$ alkyl group of "$C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α" in the definition of Substituent Group β; the $C_1$-$C_6$ alkyl moiety of "$C_1$-$C_6$ alkyl group substituted with a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α and a $C_1$-$C_6$ alkyl group and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition of Substituent Group β; and the alkyl moiety of "$C_1$-$C_6$ alkylthio group substituted with one or more groups selected from Substituent Group

α" in the definition of Substituent Group γ can be a linear or branched chain alkyl group such as a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, tert-butyl, pentyl, isopentyl, 2-methylbutyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl or 2-ethylbutyl group, and preferably it is a $C_1$-$C_4$ linear or branched chain alkyl group, more preferably a $C_1$-$C_3$ linear or branched chain alkyl group and still more preferably a methyl, ethyl, propyl or isopropyl group.

The "$C_3$-$C_8$ cycloalkyl group" in the definition of $R^6$; the $C_3$-$C_8$ cycloalkyl group of "$C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ" in the definitions of $R^a$, $R^b$ and $R^5$; the $C_3$-$C_8$ cycloalkyl group of "$C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ" which $R^3$ and $R^4$ form together with the carbon atoms to which they are bonded; the $C_3$-$C_8$ cycloalkyl group of "$C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β" in the definition of Substituent Group γ; the $C_3$-$C_8$ cycloalkyl moiety of "$C_3$-$C_8$ cycloalkyloxy group" in the definition of Substituent Group α; and the $C_3$-$C_8$ cycloalkyl moiety of "$C_3$-$C_8$ cycloalkyloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β" in the definition of Substituent Group γ can be a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl group and preferably it is a $C_3$-$C_7$ cycloalkyl group, and more preferably a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group.

The "4- to 7-membered heterocyclyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" which $R^e$ and $R^f$ form together with the nitrogen atom to which they are bonded can be, for example, azetidinyl, pyrrolidinyl, pyrrolinyl,

imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, oxazolidinyl, thiazolidinyl, oxadiazolidinyl, piperidyl, tetrahydropyridyl, dihydropyridyl, piperazinyl, morpholinyl, thiomorpholinyl or homopiperidyl, and preferably it is a 4- to 6-membered heterocyclyl group which contains 1 or 2 sulfur, oxygen and/or nitrogen atoms and particularly preferably it is azetidinyl, pyrrolidinyl, piperidyl, piperazinyl or morpholinyl.

Here, the above mentioned "5- to 7-membered heterocyclyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" may be condensed with another cyclic group (for example, a phenyl group) and such a group can be, for example, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, indolinyl or isoindolinyl.

The 5- to 7-membered heterocyclyl group of "5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definitions of $R^a$, $R^b$ and $R^5$; the 5- to 7-membered heterocyclyl group of "5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" which $R^3$ and $R^4$ form together with the carbon atoms to which they are bonded; the 5- to 7-membered heterocyclyl moiety of "5- to 7-membered heterocyclylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition of $R^5$; the 5- to 7-membered heterocyclyl moiety of "$C_1$-$C_6$ alkyl group substituted with a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α and a $C_1$-$C_6$ alkyl group and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition of

Substituent Group β; the 5- to 7-membered heterocyclyl group of "5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition of Substituent Group γ; and the 5- to 7-membered heterocyclyl moiety of "5- to 7-membered heterocyclyloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition of Substituent Group γ can be, for example, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, oxazolidinyl, dioxolanyl, thiazolidinyl, oxadiazolidinyl, piperidyl, tetrahydropyridyl, dihydropyridyl, 2H-pyranyl, 2-oxo-2H-pyranyl, tetrahydropyranyl, tetrahydrofuranyl, piperazinyl, morpholinyl, dioxanyl, thiomorpholinyl or homopiperidyl, and preferably it is a 5- to 6-membered heterocyclyl group which contains 1 or 2 sulfur, oxygen and/or nitrogen atoms, and particularly preferably it is dioxolanyl, pyrrolidinyl, piperidyl, piperazinyl or morpholinyl.

Here, the above mentioned "5- to 7-membered heterocyclyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" may be condensed with another cyclic group (for example, a phenyl group) and such a group can be, for example, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, chromanyl, indolinyl or isoindolinyl.

The "$C_6$-$C_{10}$ aryl group" in the definition of $R^6$; the $C_6$-$C_{10}$ aryl group of "$C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ" in the definitions of $R^a$, $R^b$ and $R^5$; the $C_6$-$C_{10}$ aryl group of "$C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ" which $R^3$ and $R^4$ form together with the carbon atoms to which they are bonded; the aryl moiety of "$C_7$-$C_{11}$ arylcarbonyl group

which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ" in the definition of $R^5$, the aryl moiety of "$C_6$-$C_{10}$ arylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ" and "$C_7$-$C_{11}$ aryloxycarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ"; the aryl moiety of "$C_6$-$C_{10}$ aryloxy group" in the definition of $R^6$; the "$C_6$-$C_{10}$ aryl group" in the definition of $R^e$ and $R^f$; the aryl moiety of "$C_7$-$C_{11}$ arylcarbonyl group" and "$C_6$-$C_{10}$ arylsulfonyl group" in the definition of $R^e$ and $R^f$; the $C_6$-$C_{10}$ aryl group of "$C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β" in the definition of Substituent Group γ; the aryl moiety of "$C_6$-$C_{10}$ aryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β" in the definition of Substituent Group γ; and the aryl moiety of "$C_6$-$C_{10}$ aryl - $C_1$-$C_6$ alkoxy group in which the aryl moiety may be substituted with one or more groups selected from Substituent Group α and Substituent Group β" in the definition of Substituent Group γ can be, for example, phenyl or naphthyl and is preferably phenyl.

Here, the above mentioned "$C_6$-$C_{10}$ aryl group" may be condensed with a $C_3$-$C_{10}$ cycloalkyl group (preferably a $C_5$-$C_6$ cycloalkyl group), "heterocyclyl" mentioned above or "heteroaryl" mentioned below and examples of such a group include 5-indanyl, 5-isoindolinyl, 1-oxo-2-methyl-5-isoindolinyl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, chroman-7-yl, 1,2-benzoisoxazol-6-yl, 1,3-benzodioxazol-5-yl, 2,3-dihydro-1-benzofuran-5-yl, quinolin-6-yl, isoquinolin-6-yl, 1,3-benzothiazol-6-yl and indol-5-yl.

The 5- to 7-membered heteroaryl group of "5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent

Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definitions of $R^a$, $R^b$ and $R^5$; the 5- to 7-membered heteroaryl group of "5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" which $R^3$ and $R^4$ form together with the carbon atoms to which they are bonded; the 5- to 7-membered heteroaryl moiety of "5- to 7-membered heteroarylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" and "5- to 7-membered heteroarylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition of $R^5$; the "5- to 7-membered heteroaryl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definitions of $R^e$ and $R^f$; the 5- to 7-membered heteroaryl moiety of "5- to 7-membered heteroarylcarbonyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" and "5- to 7-membered heteroarylsulfonyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definitions of $R^e$ and $R^f$; the 5- to 7-membered heteroaryl group of "5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition of Substituent Group γ; and the 5- to 7-membered heteroaryl moiety of "5- to 7-membered heteroaryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition of Substituent Group γ can be, for example, furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl,

pyrimidinyl, pyrazinyl or azepinyl and preferably it is a 5- to 6-membered heteroaryl group which contains 1 or 2 sulfur, oxygen and/or nitrogen atoms such as furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl.

Here, the above mentioned "5- to 7-membered heteroaryl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" may be condensed with another cyclic group [for example, a $C_6$-$C_{10}$ aryl or $C_3$-$C_8$ cycloalkyl group (preferably, a $C_5$-$C_6$ cycloalkyl group)], and such a group can be indolyl, benzofuranyl, benzothienyl, quinolyl, isoquinolyl, quinazolinyl, 5,6,7,8-tetrahydroquinolyl or 5,6,7,8-tetrahydroisoquinolyl.

The $C_1$-$C_6$ alkoxy group of "$C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group γ" in the definitions of $R^3$ and $R^4$; the alkoxy moiety of "$C_2$-$C_7$ alkoxycarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ" in the definition of $R^5$; the "$C_1$-$C_6$ alkoxy group" in the definitions of $R^6$ and Substituent Group α; the "$C_1$-$C_6$ alkoxy group" in the definitions of $R^e$ and $R^f$; the $C_1$-$C_6$ alkoxy moiety of " $C_1$-$C_6$ alkoxyimino group" in the definition of Substituent Group α; and the $C_1$-$C_6$ alkoxy group of " $C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group α" in the definition of Substituent Group γ is one or more groups in which an oxygen atom is bonded to the above "$C_1$-$C_6$ alkyl group", more preferably it is a $C_1$-$C_4$ linear or branched chain alkoxy group, more preferably it is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy or tert-butoxy, still more preferably it is methoxy, ethoxy, propoxy, isopropoxy or butoxy, and particularly preferably it is methoxy or ethoxy.

The $C_2$-$C_6$ alkenyl group of "$C_2$-$C_6$ alkenyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ" in the definition of $R^5$ can be a linear or branched chain alkenyl group such as a

vinyl, 2-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-ethyl-2-propenyl, 2-butenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 1-ethyl-2-butenyl, 3-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 1-ethyl-3-butenyl, 2-pentenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-pentenyl, 1-methyl-3-pentenyl, 2-methyl-3-pentenyl, 4-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl or 5-hexenyl group and preferably it is a $C_2$-$C_4$ linear or branched chain alkyl group, more preferably it is vinyl or 2-propenyl, and particularly preferably it is vinyl.

The "$C_2$-$C_7$ alkylcarbonyl group" in the definitions of $R^e$ and $R^f$; and the $C_2$-$C_7$ alkylcarbonyl group of "$C_2$-$C_7$ alkylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ" in the definition of $R^5$ is a group in which carbonyl is bonded to the above "$C_1$-$C_6$ alkyl group", and preferably it is a $C_2$-$C_5$ linear or branched chain alkylcarbonyl group, more preferably it is acetyl, propionyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl, isobutylcarbonyl or tert-butylcarbonyl, still more preferably it is acetyl, propionyl, propylcarbonyl, isopropylcarbonyl or butylcarbonyl, and particularly preferably it is acetyl or propionyl.

The 5- to 7-membered heterocyclylcarbonyl group of "5- to 7-membered heterocyclylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms " in the definition of $R^5$ is a group in which carbonyl is bonded to the above "5- to 7-membered heterocyclyl group", and preferably it is a 5- to 6-membered heterocyclylcarbonyl group which contains 1 or 2 sulfur, oxygen and/or nitrogen atoms, and particularly preferably it is piperidylcarbonyl, piperazinylcarbonyl or morpholinylcarbonyl.

The $C_7$-$C_{11}$ arylcarbonyl group" in the definitions of $R^e$ and $R^f$; and the $C_7$-$C_{11}$ arylcarbonyl group of "$C_7$-$C_{11}$ arylcarbonyl group which may be substituted with one

or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ" in the definition of $R^5$ is a group in which carbonyl is bonded to the above "$C_6$-$C_{10}$ aryl group", and preferably it is benzoyl.

The "5- to 7-membered heteroarylcarbonyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definitions of $R^e$ and $R^f$; and the "5- to 7-membered heteroarylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definitions of $R^5$ is a group in which carbonyl is bonded to the above "5- to 7-membered heteroaryl group", and preferably it is 5- to 6-membered heteroarylcarbonyl which contains 1 or 2 sulfur, oxygen and/or nitrogen atoms.

The "$C_1$-$C_6$ alkylsulfonyl group" in the definitions of Substituent Group α, $R^e$ and $R^f$; and the $C_1$-$C_6$ alkylsulfonyl group of "$C_1$-$C_6$ alkylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ" in the definition of $R^5$ is a group in which sulfonyl is bonded to the above "$C_1$-$C_6$ alkyl group", and preferably it is a $C_1$-$C_4$ linear or branched chain alkylsulfonyl group, more preferably it is methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl or tert-butylsulfonyl, still more preferably it is methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl or butylsulfonyl, and particularly preferably it is methylsulfonyl or ethylsulfonyl.

The "$C_6$-$C_{10}$ arylsulfonyl group" in the definitions of Substituent Group, $R^e$ and $R^f$; and the $C_6$-$C_{10}$ arylsulfonyl group of "$C_6$-$C_{10}$ arylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ" in the definition of $R^5$ is a group in which sulfonyl is bonded to the above "$C_6$-$C_{10}$ aryl group", and preferably it phenylsulfonyl.

The "5- to 7-membered heteroarylsulfonyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definitions of $R^e$ and $R^f$; and the 5- to 7-membered heteroarylsulfonyl group of "5- to 7-membered heteroarylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition $R^5$ is a group in which sulfonyl is bonded to the above "5- to 7-membered heteroaryl group", and preferably it is 5- to 6-membered heteroarylsulfonyl which contains 1 or 2 sulfur, oxygen and/or nitrogen atoms.

The "$C_2$-$C_7$ alkoxycarbonyl group" in the definitions of $R^e$ and $R^f$; and the $C_2$-$C_7$ alkoxycarbonyl group of "$C_2$-$C_7$ alkoxycarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ" in the definition of $R^5$ is a group in which carbonyl is bonded to the above "$C_1$-$C_6$ alkoxy group", and preferably it is a $C_2$-$C_5$ linear or branched chain alkoxycarbonyl group, more preferably it is methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl or tert-butoxycarbonyl, still more preferably it is methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl or tert-butoxycarbonyl, and particularly preferably it is methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl.

The"$C_6$-$C_{10}$ aryloxy group" in the definition of $R^6$; and the $C_6$-$C_{10}$ aryloxy group of "$C_6$-$C_{10}$ aryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β" in the definition of Substituent Group γ is a group in which an oxygen atom is bonded to the above "$C_6$-$C_{10}$ aryl group", and preferably it is phenoxy.

The $C_7$-$C_{11}$ aryloxycarbonyl group of "$C_7$-$C_{11}$ aryloxycarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ" in the definition of $R^5$ is a group in

which carbonyl is bonded to the above "$C_6$-$C_{10}$ aryloxy group", and preferably it is phenoxycarbonyl.

The "halogen atom" in the definition of Substituent Group α is a fluorine atom, a chlorine atom, a bromine atom or an iodine atom and preferably it is a fluorine atom or a chlorine atom.

The "$C_1$-$C_6$ halogenated alkyl group" in the definition of $R^6$ is a group in which one or two or more hydrogen atoms in the above "$C_1$-$C_6$ alkyl group" is substituted with a "halogen atom" mentioned above, and preferably it is a $C_1$-$C_4$ alkyl halide group, more preferably it is trifluoromethyl, trichloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, fluoromethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2-bromoethyl, 2-chloroethyl, 2-fluoroethyl or 2,2-dibromoethyl, still more preferably it is trifluoromethyl, trichloromethyl, difluoromethyl or fluoromethyl, and the most preferably it is trifluoromethyl.

The "$C_1$-$C_6$ halogenated alkoxy group" in the definition of Substituent Group α is a group in which one or two or more hydrogen atoms in the above "$C_1$-$C_6$ alkoxy group" is substituted with a "halogen atom" mentioned above, and preferably it is a $C_1$-$C_4$ halogenated alkoxy group, more preferably it is trifluoromethyloxy, trichloromethyloxy, difluoromethyloxy, dichloromethyloxy, dibromomethyloxy, fluoromethyloxy, 2,2,2-trichloroethyloxy, 2,2,2-trifluoroethyloxy, 2-bromoethyloxy, 2-chloroethyloxy, 2-fluoroethyloxy or 2,2-dibromoethyloxy, and still more preferably it is trifluoromethyloxy, trichloromethyloxy, difluoromethyloxy or fluoromethyloxy.

The "$C_1$-$C_6$ alkylthio group" in the definition of Substituent Group α; and the $C_1$-$C_6$ alkylthio group of "$C_1$-$C_6$ alkylthio group substituted with one or more groups selected from Substituent Group α" in the definition of Substituent Group γ is a group in which a sulfur atom is bonded to the above "$C_1$-$C_6$ alkyl group", and preferably it is a $C_1$-$C_4$ linear or branched chain alkylthio group, more preferably it is

methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio or tert-butylthio, still more preferably it is methylthio, ethylthio, propylthio, isopropylthio or butylthio, and particularly preferably it is methylthio or ethylthio.

The "$C_1$-$C_6$ alkylsulfinyl group" in the definition of Substituent Group α is a group in which sulfinyl is bonded to the above "$C_1$-$C_6$ alkyl group", and preferably it is a $C_1$-$C_4$ linear or branched chain alkylsulfinyl group, more preferably it is methylsulfinyl, ethylsulfinyl, propylsulphinyl, isopropylsulphinyl, butylsulfinyl, isobutylsulfinyl or tert-butylsulfinyl, still more preferably it is methylsulfinyl, ethylsulfinyl, propylsulphinyl, isopropylsulfinyl or butylsulfinyl, and particularly preferably it is methylsulfinyl or ethylsulfinyl.

The "$C_3$-$C_8$ cycloalkyloxy group" in the definition of Substituent Group α; and the $C_3$-$C_8$ cycloalkyloxy group of "$C_3$-$C_8$ cycloalkyloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β" in the definition of Substituent Group γ is a group in which an oxygen atom is bonded to the above "$C_3$-$C_8$ cycloalkyl group", and preferably it is a $C_3$-$C_7$ cycloalkyloxy group, and more preferably it is cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy.

The 5- to 7-membered heterocyclyloxy group of "5- to 7-membered heterocyclyloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition of Substituent Group γ is a group in which an oxygen atom is bonded to the above "5- to 7-membered heterocyclyl group", and preferably it is a 5- to 6-membered heterocyclyloxy group which contains 1 or 2 sulfur, oxygen and/or nitrogen atoms, and particularly preferably it is piperidyloxy.

The 5- to 7-membered heteroaryloxy group of "5- to 7-membered heteroaryloxy group which may be substituted with one or more groups selected

from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms" in the definition of Substituent Group γ is a group in which an oxygen atom is bonded to the above "5- to 7-membered heteroaryl which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms", and preferably it is a 5- to 6-member heteroaryloxy group which contains 1 or 2 sulfur, oxygen and/or nitrogen atoms, and more preferably it is furyloxy, thienyloxy, pyrrolyloxy, pyrazolyloxy, imidazolyloxy, oxazolyloxy, isoxazolyloxy, thiazolyloxy, isothiazolyloxy, pyridyloxy, pyridazinyloxy, pyrimidinyloxy or pyrazinyloxy.

The $C_6$-$C_{10}$ aryl - $C_1$-$C_6$ alkoxy group of "$C_6$-$C_{10}$ aryl - $C_1$-$C_6$ alkoxy group in which the aryl moiety may be substituted with one or more groups selected from Substituent Group α and Substituent Group β" in the definition of Substituent Group γ is the above "$C_1$-$C_6$ alkoxy group" substituted with a "$C_6$-$C_{10}$ aryl group" mentioned above, and preferably it is benzyloxy, phenethyloxy or 3-phenylpropyloxy, and particularly preferably it is benzyloxy.

Since compound (I) of the present invention can be converted to a salt by reacting with an acid when it has a basic functional group such as an amino group or with a base when it has an acidic functional group such as a carboxyl group, the "pharmacologically acceptable salt thereof" refers to such a salt.

The salt based on a basic functional group can be, for example, an inorganic acid salt such as a hydrohalide such as hydrochloride, hydrobromide or hydriodide, nitrate, perchlorate, sulfate or phosphate; an organic salt such as a lower alkanesulfonate such as methanesulfonate, trifluoromethanesulfonate or ethanesulfonate, an aryl sulfonate such as benzenesulfonate or p-toluenesulfonate, or a carboxylate such as acetate, malate, fumarate, succinate, citrate, ascorbate, tartrate, oxalate or maleate; or it can be an amino acid salt such as glycinate, lysinate, argininate, ornithinate, glutamate or aspartate.

The salt based on an acid functional group can be, for example, a metal salt such as an alkali metal salt such as a sodium salt, potassium salt or lithium salt, an alkaline earth metal salt such as a calcium salt or magnesium salt, an aluminium salt or an iron salt; an ammonium salt; an organic amine salt such as a t-octylamine salt, dibenzylamine salt, morpholine salt, glucosamine salt, phenylglycine alkyl ester salt, diaminoethane salt, N-methylglucamine salt, guanidine salt, diethylamine salt, triethylamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, chloroprocaine salt, procaine salt, diethanolamine salt, N-benzylphenethylamine salt, piperazine salt, tetramethylammonium salt or tris(hydroxymethyl)aminomethane salt; or it can be an amino acid salt such as glycine salt, lysine salt, arginine salt, ornithine salt, glutamate or aspartate.

The compounds having general formula (I) of the present invention or pharmacologically acceptable salt thereof when allowed to stand in the atmosphere or to recrystallize may absorb water or adsorb water to form hydrates and such hydrates are also included in the present invention.

Among the compounds having general formula (I) of the present invention, there may be optical isomers due to an asymmetric centre in the molecule. For the compounds of the present invention, it should be noted that these isomers and mixtures thereof are represented by a single formula, i.e. general formula (I). Therefore, the present invention encompasses these isomers and mixtures of these isomers in any ratio.

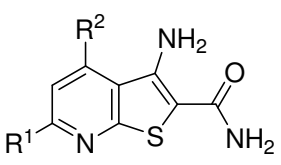
Specific examples of the compound having general formula (I) of the present invention include compounds described in the following Table 1 to Table 3 for exemplified compounds.

Here, in Table 1 to Table 3, "Ac" represents acetyl, "Aze" represents azetidino, "perhydro-1-Azep" represents perhydroazepin-1-yl, "perhydro-1-Azoc" represents perhydroazocin-1-yl, "Bn" represents benzyl, "Bu" represents butyl, "iBu" represents

isobutyl, "tBu" represents tert-butyl, "BzIox" represents 1,2-benzisoxazolyl, "BzDioxa" represents 1,4-benzodioxanyl, "BzDioxo" represents 1,3-benzodioxolanyl, "BzFur" represents 1-benzofuranyl, "Bzhy" represents benzhydryl, "BzOxaz" represents 1,3-benzoxazolyl, "BzThaz" represents 1,3-benzothiazolyl, "Chr" represents chromanyl, "Dioxa" represents 1,3-dioxanyl, "Dioxo" represents 1,3-dioxolanyl, "Et" represents ethyl, "Fur" represents furanyl, "cHep" represents cycloheptyl, "cHx" represents cyclohexyl, "IIndn" represents isoindolinyl, "Ind" represents indolyl, "Iqui" represents isoquinolyl, "decahydro-2-Iqui" represents 1,2,3,4,5,6,7,8,9,10-decahydroisoquinolin-2-yl, "1,2,3,4-tetrahydro-2-Iqui" represents 1,2,3,4-tetrahydroisoquinolin-2-yl, "Me" represents methyl, "Mor" represents morpholin-4-yl, "Oxaz" represents oxazolyl, "1,4-Oxazep" represents 1,4-oxazepin-4-yl, "Oxazn" represents oxazolynyl, "Ph" represents phenyl, "Phet" represents phenethyl, "Pip" represents piperidin-4-yl, "3,4-dehydro-Pip" represents 3,4-dehydropiperidin-4-yl, "Pipo" represents piperidino, "Pipra" represents piperazino, "cPn" represents cyclopentyl, "neoPn" represents neopentyl, "Pr" represents propyl, "iPr" represents isopropyl, "Py" represents pyridyl, "Pydz" represents pyridazinyl, "Pym" represents pyrimidyl, "Pyrld" represents pyrrolidin-1-yl, "Qui" represents quinolyl, "Qunz" represents quinazolinyl, "Thaz" represents thiazolyl, "Thazn" represents thiazolinyl, "Thi" represents thienyl, "1,4-Thiazep" represents 1,4-thiazepin-4-yl, and "Thmor" represents thiomorpholin-4-yl.

Table 1

[Formula 5]




(I)

| Compound Number | $R^1$ | $R^2$ |
|---|---|---|
| 1-1 | H | MeO |
| 1-2 | H | EtO |
| 1-3 | H | iPrO |
| 1-4 | H | BnO |
| 1-5 | H | (HOOC)-$CH_2$O |
| 1-6 | H | cPnO |
| 1-7 | H | cHxO |
| 1-8 | H | cHepO |
| 1-9 | H | MeS |
| 1-10 | H | EtS |
| 1-11 | H | iPrS |
| 1-12 | H | BnS |
| 1-13 | H | cHxS |
| 1-14 | H | cHepS |
| 1-15 | H | Pyrld |
| 1-16 | H | Pip |
| 1-17 | H | 3-Me-Pip |
| 1-18 | H | 4-Me-Pip |
| 1-19 | H | 4-Bn-Pip |
| 1-20 | H | 3-(HO-$CH_2$)-Pip |
| 1-21 | H | 3-(MeO-$CH_2$)-Pip |
| 1-22 | H | 3-(EtO-$CH_2$)-Pip |
| 1-23 | H | 3-(PrO-$CH_2$)-Pip |

| | | |
|---|---|---|
| 1-24 | H | 3-(BnO-$CH_2$)-Pip |
| 1-25 | H | 3-Ph-Pip |
| 1-26 | H | 4-Ph-Pip |
| 1-27 | H | 3-HO-Pip |
| 1-28 | H | 3-MeO-Pip |
| 1-29 | H | 3-EtO-Pip |
| 1-30 | H | 3-PrO-Pip |
| 1-31 | H | 3-BnO-Pip |
| 1-32 | H | 4-HO-Pip |
| 1-33 | H | 3-AcO-Pip |
| 1-34 | H | 4-AcO-Pip |
| 1-35 | H | 1,2,3,4-tetrahydro-2-Iqui |
| 1-36 | H | decahydro-2-Iqui |
| 1-37 | H | 3,4-dehydro-Pip |
| 1-38 | H | 4-Ph-3,4-dehydro-1-Pip |
| 1-39 | H | perhydro-1-Azep |
| 1-40 | H | perhydro-1-Azoc |
| 1-41 | H | Mor |
| 1-42 | H | 2,6-diMe-Mor |
| 1-43 | H | 1,4-Oxazep |
| 1-44 | H | Thmor |
| 1-45 | H | 1-Oxo-Thmor |
| 1-46 | H | 1,4-Thiazep |
| 1-47 | H | 1-Oxo-1,4-Thiazep |
| 1-48 | Me | MeO |
| 1-49 | Me | EtO |
| 1-50 | Me | iPrO |

| | | |
|---|---|---|
| 1-51 | Me | BnO |
| 1-52 | Me | (HOOC)-$CH_2O$ |
| 1-53 | Me | cPnO |
| 1-54 | Me | cHxO |
| 1-55 | Me | cHepO |
| 1-56 | Me | MeS |
| 1-57 | Me | EtS |
| 1-58 | Me | iPrS |
| 1-59 | Me | BnS |
| 1-60 | Me | cHxS |
| 1-61 | Me | cHepS |
| 1-62 | Me | Pyrld |
| 1-63 | Me | Pip |
| 1-64 | Me | 3-Me-Pip |
| 1-65 | Me | 4-Me-Pip |
| 1-66 | Me | 4-Bn-Pip |
| 1-67 | Me | 3-(HO-$CH_2$)-Pip |
| 1-68 | Me | 3-(MeO-$CH_2$)-Pip |
| 1-69 | Me | 3-(EtO-$CH_2$)-Pip |
| 1-70 | Me | 3-(PrO-$CH_2$)-Pip |
| 1-71 | Me | 3-(BnO-$CH_2$)-Pip |
| 1-72 | Me | 3-Ph-Pip |
| 1-73 | Me | 4-Ph-Pip |
| 1-74 | Me | 3-HO-Pip |
| 1-75 | Me | 3-MeO-Pip |
| 1-76 | Me | 3-EtO-Pip |
| 1-77 | Me | 3-PrO-Pip |

| | | |
|---|---|---|
| 1-78 | Me | 3-BnO-Pip |
| 1-79 | Me | 4-HO-Pip |
| 1-80 | Me | 3-AcO-Pip |
| 1-81 | Me | 4-AcO-Pip |
| 1-82 | Me | 1,2,3,4-tetrahydro-2-Iqui |
| 1-83 | Me | decahydro-2-Iqui |
| 1-84 | Me | 3,4-dehydro-Pip |
| 1-85 | Me | 4-Ph-3,4-dehydro-1-Pip |
| 1-86 | Me | perhydro-1-Azep |
| 1-87 | Me | perhydro-1-Azoc |
| 1-88 | Me | Mor |
| 1-89 | Me | 2,6-diMe-Mor |
| 1-90 | Me | 1,4-Oxazep |
| 1-91 | Me | Thmor |
| 1-92 | Me | 1-Oxo-Thmor |
| 1-93 | Me | 1,4-Thiazep |
| 1-94 | Me | 1-Oxo-1,4-Thiazep |
| 1-95 | H | 3-[HO-$(CH_2)_2$]-Pip |
| 1-96 | H | 3-[HO-$(CH_2)_3$]-Pip |
| 1-97 | H | 3-[HO-$(CH_2)_4$]-Pip |
| 1-98 | H | 3-[HO-$(CH_2)_5$]-Pip |
| 1-99 | H | 3-[HO-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-100 | H | 3-[HO-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-101 | H | 3-[HO-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-102 | H | 3-[HO-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-103 | H | 3-[HO-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-104 | H | 3-[HO-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |

| | | |
|---|---|---|
| 1-105 | H | 3-[HO-$(CH_2)_4$-O-$CH_2$]-Pip |
| 1-106 | H | 3-[HO-$(CH_2)_4$-O-$(CH_2)_2$]-Pip |
| 1-107 | H | 3-[HO-$(CH_2)_4$-O-$(CH_2)_3$]-Pip |
| 1-108 | H | 3-[MeO-$(CH_2)_2$]-Pip |
| 1-109 | H | 3-[MeO-$(CH_2)_3$]-Pip |
| 1-110 | H | 3-[MeO-$(CH_2)_4$]-Pip |
| 1-111 | H | 3-[MeO-$(CH_2)_5$]-Pip |
| 1-112 | H | 3-[MeO-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-113 | H | 3-[MeO-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-114 | H | 3-[MeO-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-115 | H | 3-[MeO-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-116 | H | 3-[MeO-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-117 | H | 3-[MeO-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-118 | H | 3-[MeO-$(CH_2)_4$-O-$CH_2$]-Pip |
| 1-119 | H | 3-[MeO-$(CH_2)_4$-O-$(CH_2)_2$]-Pip |
| 1-120 | H | 3-[MeO-$(CH_2)_4$-O-$(CH_2)_3$]-Pip |
| 1-121 | H | 3-[EtO-$(CH_2)_2$]-Pip |
| 1-122 | H | 3-[EtO-$(CH_2)_3$]-Pip |
| 1-123 | H | 3-[EtO-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-124 | H | 3-[EtO-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-125 | H | 3-[EtO-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-126 | H | 3-[PrO-$(CH_2)_2$]-Pip |
| 1-127 | H | 3-[PrO-$(CH_2)_3$]-Pip |
| 1-128 | H | 3-[BnO-$(CH_2)_2$]-Pip |
| 1-129 | H | 3-[BnO-$(CH_2)_3$]-Pip |
| 1-130 | H | 3-[PhO-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-131 | H | 3-[PhO-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |

| | | |
|---|---|---|
| 1-132 | H | 3-[PhO-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-133 | H | 3-[$H_2N$-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-134 | H | 3-[$H_2N$-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-135 | H | 3-[$H_2N$-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-136 | H | 3-[$H_2N$-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-137 | H | 3-[$H_2N$-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-138 | H | 3-[$H_2N$-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-139 | H | 3-[$H_2N$-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-140 | H | 3-[$H_2N$-$(CH_2)_2$-O-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-141 | H | 3-[$Me_2N$-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-142 | H | 3-[$Me_2N$-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-143 | H | 3-[$Me_2N$-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-144 | H | 3-[$Me_2N$-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-145 | H | 3-[$Me_2N$-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-146 | H | 3-[$Me_2N$-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-147 | H | 3-[$Me_2N$-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-148 | H | 3-[$Me_2N$-$(CH_2)_2$-O-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-149 | H | 3-(CN-$CH_2$-O-$CH_2$)-Pip |
| 1-150 | H | 3-[CN-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-151 | H | 3-[CN-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-152 | H | 3-[CN-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-153 | H | 3-[CN-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-154 | H | 3-[CN-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-155 | H | 3-($Me_2NCO$-$CH_2$-O-$CH_2$)-Pip |
| 1-156 | H | 3-[$Me_2NCO$-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-157 | H | 3-[$Me_2NCO$-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-158 | H | 3-[$Me_2NCO$-$(CH_2)_2$-O-$CH_2$]-Pip |

| | | |
|---|---|---|
| 1-159 | H | 3-[$Me_2NCO$-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-160 | H | 3-[$Me_2NCO$-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-161 | H | 3-[$Me_2NCO$-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-162 | H | 3-[$Me_2NCO$-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-163 | H | 3-[$Me_2NCO$-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-164 | H | 3-($Et_2NCO$-$CH_2$-O-$CH_2$)-Pip |
| 1-165 | H | 3-[$Et_2NCO$-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-166 | H | 3-[$Et_2NCO$-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-167 | H | 3-[$Et_2NCO$-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-168 | H | 3-[$Et_2NCO$-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-169 | H | 3-[$Et_2NCO$-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-170 | H | 3-[$Et_2NCO$-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-171 | H | 3-[$Et_2NCO$-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-172 | H | 3-[$Et_2NCO$-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-173 | H | 3-[AcNH-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-174 | H | 3-[AcNH-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-175 | H | 3-[AcNH-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-176 | H | 3-[AcNH-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-177 | H | 3-[AcNH-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-178 | H | 3-[AcNH-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-179 | H | 3-[AcNH-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-180 | H | 3-[AcNH-$(CH_2)_2$-O-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-181 | H | 3-[Me-$(CH_2)_4$-CONH-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-182 | H | 3-[BocNH-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-183 | H | 3-[NC-$(CH_2)_2$-CONH-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-184 | H | 3-($H_2N$-$CH_2$)-Pip |
| 1-185 | H | 3-[HO-$(CH_2)_2$-NH-$CH_2$]-Pip |

| | | |
|---|---|---|
| 1-186 | H | 3-(BocNH-$CH_2$)-Pip |
| 1-187 | H | 3-(MeNH-$CH_2$)-Pip |
| 1-188 | H | 3-[Me-$(CH_2)_3$-NH-$CH_2$]-Pip |
| 1-189 | H | 3-($Me_2N$-$CH_2$)-Pip |
| 1-190 | H | 2-(MeO-$CH_2$)-Mor |
| 1-191 | H | 3-[$Et_2N$-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-192 | H | 3-[$Et_2N$-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-193 | H | 3-[$Et_2N$-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-194 | H | 3-[$Et_2N$-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-195 | H | 3-[$Et_2N$-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-196 | H | 3-[$Et_2N$-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-197 | H | 3-[$Et_2N$-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-198 | H | 3-[Pyrld-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-199 | H | 3-[Pyrld-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-200 | H | 3-[Pyrld-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-201 | H | 3-[Pyrld-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-202 | H | 3-[Pyrld-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-203 | H | 3-[Pyrld-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-204 | H | 3-[Pyrld-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-205 | H | 3-[Mor-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-206 | H | 3-[Mor-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-207 | H | 3-[Mor-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-208 | H | 3-[Mor-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-209 | H | 3-[Mor-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-210 | H | 3-[Mor-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-211 | H | 3-[Mor-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-212 | H | 3-[Pipo-$(CH_2)_2$-O-$CH_2$]-Pip |

| | | |
|---|---|---|
| 1-213 | H | 3-[Pipo-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-214 | H | 3-[Pipo-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-215 | H | 3-[Pipo-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-216 | H | 3-[Pipo-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-217 | H | 3-[Pipo-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-218 | H | 3-[Pipo-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-219 | H | 3-[(4-Me-Pipra)-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-220 | H | 3-[(4-Me-Pipra)-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-221 | H | 3-[(4-Me-Pipra)-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-222 | H | 3-[(4-Me-Pipra)-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-223 | H | 3-[(4-Me-Pipra)-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-224 | H | 3-[(4-Me-Pipra)-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-225 | H | 3-[(4-Me-Pipra)-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-226 | H | 3-(Pyrld-CO-$CH_2$-O-$CH_2$)-Pip |
| 1-227 | H | 3-[Pyrld-CO-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-228 | H | 3-[Pyrld-CO-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-229 | H | 3-(Mor-CO-$CH_2$-O-$CH_2$)-Pip |
| 1-230 | H | 3-[Mor-CO-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-231 | H | 3-[Mor-CO-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-232 | H | 3-(Pipo-CO-$CH_2$-O-$CH_2$)-Pip |
| 1-233 | H | 3-[Pipo-CO-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-234 | H | 3-[Pipo-CO-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-235 | H | 3-[(4-Me-Pipra)-CO-$CH_2$-O-$CH_2$]-Pip |
| 1-236 | H | 3-[(4-Me-Pipra)-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-237 | H | 3-[(4-Me-Pipra)-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-238 | Me | 3-[HO-$(CH_2)_2$]-Pip |
| 1-239 | Me | 3-[HO-$(CH_2)_3$]-Pip |

| | | |
|---|---|---|
| 1-240 | Me | 3-[HO-$(CH_2)_4$]-Pip |
| 1-241 | Me | 3-[HO-$(CH_2)_5$]-Pip |
| 1-242 | Me | 3-[HO-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-243 | Me | 3-[HO-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-244 | Me | 3-[HO-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-245 | Me | 3-[HO-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-246 | Me | 3-[HO-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-247 | Me | 3-[HO-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-248 | Me | 3-[HO-$(CH_2)_4$-O-$CH_2$]-Pip |
| 1-249 | Me | 3-[HO-$(CH_2)_4$-O-$(CH_2)_2$]-Pip |
| 1-250 | Me | 3-[HO-$(CH_2)_4$-O-$(CH_2)_3$]-Pip |
| 1-251 | Me | 3-[MeO-$(CH_2)_2$]-Pip |
| 1-252 | Me | 3-[MeO-$(CH_2)_3$]-Pip |
| 1-253 | Me | 3-[MeO-$(CH_2)_4$]-Pip |
| 1-254 | Me | 3-[MeO-$(CH_2)_5$]-Pip |
| 1-255 | Me | 3-[MeO-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-256 | Me | 3-[MeO-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-257 | Me | 3-[MeO-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-258 | Me | 3-[MeO-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-259 | Me | 3-[MeO-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-260 | Me | 3-[MeO-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-261 | Me | 3-[MeO-$(CH_2)_4$-O-$CH_2$]-Pip |
| 1-262 | Me | 3-[MeO-$(CH_2)_4$-O-$(CH_2)_2$]-Pip |
| 1-263 | Me | 3-[MeO-$(CH_2)_4$-O-$(CH_2)_3$]-Pip |
| 1-264 | Me | 3-[EtO-$(CH_2)_2$]-Pip |
| 1-265 | Me | 3-[EtO-$(CH_2)_3$]-Pip |
| 1-266 | Me | 3-[EtO-$(CH_2)_2$-O-$CH_2$]-Pip |

| | | |
|---|---|---|
| 1-267 | Me | 3-[EtO-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-268 | Me | 3-[EtO-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-269 | Me | 3-[PrO-$(CH_2)_2$]-Pip |
| 1-270 | Me | 3-[PrO-$(CH_2)_3$]-Pip |
| 1-271 | Me | 3-[BnO-$(CH_2)_2$]-Pip |
| 1-272 | Me | 3-[BnO-$(CH_2)_3$]-Pip |
| 1-273 | Me | 3-[PhO-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-274 | Me | 3-[PhO-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-275 | Me | 3-[PhO-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-276 | Me | 3-[$H_2N$-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-277 | Me | 3-[$H_2N$-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-278 | Me | 3-[$H_2N$-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-279 | Me | 3-[$H_2N$-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-280 | Me | 3-[$H_2N$-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-281 | Me | 3-[$H_2N$-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-282 | Me | 3-[$H_2N$-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-283 | Me | 3-[$H_2N$-$(CH_2)_2$-O-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-284 | Me | 3-[$Me_2N$-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-285 | Me | 3-[$Me_2N$-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-286 | Me | 3-[$Me_2N$-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-287 | Me | 3-[$Me_2N$-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-288 | Me | 3-[$Me_2N$-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-289 | Me | 3-[$Me_2N$-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-290 | Me | 3-[$Me_2N$-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-291 | Me | 3-[$Me_2N$-$(CH_2)_2$-O-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-292 | Me | 3-(CN-$CH_2$-O-$CH_2$)-Pip |
| 1-293 | Me | 3-[CN-$CH_2$-O-$(CH_2)_2$]-Pip |

| | | |
|---|---|---|
| 1-294 | Me | 3-[CN-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-295 | Me | 3-[CN-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-296 | Me | 3-[CN-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-297 | Me | 3-[CN-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-298 | Me | 3-($Me_2$NCO-$CH_2$-O-$CH_2$)-Pip |
| 1-299 | Me | 3-[$Me_2$NCO-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-300 | Me | 3-[$Me_2$NCO-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-301 | Me | 3-[$Me_2$NCO-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-302 | Me | 3-[$Me_2$NCO-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-303 | Me | 3-[$Me_2$NCO-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-304 | Me | 3-[$Me_2$NCO-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-305 | Me | 3-[$Me_2$NCO-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-306 | Me | 3-[$Me_2$NCO-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-307 | Me | 3-($Et_2$NCO-$CH_2$-O-$CH_2$)-Pip |
| 1-308 | Me | 3-[$Et_2$NCO-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-309 | Me | 3-[$Et_2$NCO-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-310 | Me | 3-[$Et_2$NCO-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-311 | Me | 3-[$Et_2$NCO-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-312 | Me | 3-[$Et_2$NCO-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-313 | Me | 3-[$Et_2$NCO-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-314 | Me | 3-[$Et_2$NCO-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-315 | Me | 3-[$Et_2$NCO-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-316 | Me | 3-[AcNH-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-317 | Me | 3-[AcNH-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-318 | Me | 3-[AcNH-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-319 | Me | 3-[AcNH-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-320 | Me | 3-[AcNH-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |

| | | |
|---|---|---|
| 1-321 | Me | 3-[AcNH-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-322 | Me | 3-[AcNH-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-323 | Me | 3-[AcNH-$(CH_2)_2$-O-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-324 | Me | 3-[Me-$(CH_2)_4$-CONH-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-325 | Me | 3-[BocNH-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-326 | Me | 3-[NC-$(CH_2)_2$-CONH-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-327 | Me | 3-($H_2N$-$CH_2$)-Pip |
| 1-328 | Me | 3-[HO-$(CH_2)_2$-NH-$CH_2$]-Pip |
| 1-329 | Me | 3-(BocNH-$CH_2$)-Pip |
| 1-330 | Me | 3-(MeNH-$CH_2$)-Pip |
| 1-331 | Me | 3-[Me-$(CH_2)_3$-NH-$CH_2$]-Pip |
| 1-332 | Me | 3-($Me_2N$-$CH_2$)-Pip |
| 1-333 | Me | 2-(MeO-$CH_2$)-Mor |
| 1-334 | Me | 3-[$Et_2N$-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-335 | Me | 3-[$Et_2N$-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-336 | Me | 3-[$Et_2N$-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-337 | Me | 3-[$Et_2N$-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-338 | Me | 3-[$Et_2N$-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-339 | Me | 3-[$Et_2N$-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-340 | Me | 3-[$Et_2N$-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-341 | Me | 3-[Pyrld-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-342 | Me | 3-[Pyrld-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-343 | Me | 3-[Pyrld-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-344 | Me | 3-[Pyrld-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-345 | Me | 3-[Pyrld-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-346 | Me | 3-[Pyrld-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-347 | Me | 3-[Pyrld-$(CH_2)_2$-S-$CH_2$]-Pip |

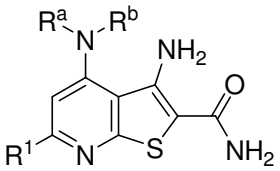
| | | |
|---|---|---|
| 1-348 | Me | 3-[Mor-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-349 | Me | 3-[Mor-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-350 | Me | 3-[Mor-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-351 | Me | 3-[Mor-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-352 | Me | 3-[Mor-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-353 | Me | 3-[Mor-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-354 | Me | 3-[Mor-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-355 | Me | 3-[Pipo-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-356 | Me | 3-[Pipo-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-357 | Me | 3-[Pipo-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-358 | Me | 3-[Pipo-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-359 | Me | 3-[Pipo-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-360 | Me | 3-[Pipo-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-361 | Me | 3-[Pipo-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-362 | Me | 3-[(4-Me-Pipra)-$(CH_2)_2$-O-$CH_2$]-Pip |
| 1-363 | Me | 3-[(4-Me-Pipra)-$(CH_2)_2$-O-$(CH_2)_2$]-Pip |
| 1-364 | Me | 3-[(4-Me-Pipra)-$(CH_2)_2$-O-$(CH_2)_3$]-Pip |
| 1-365 | Me | 3-[(4-Me-Pipra)-$(CH_2)_3$-O-$CH_2$]-Pip |
| 1-366 | Me | 3-[(4-Me-Pipra)-$(CH_2)_3$-O-$(CH_2)_2$]-Pip |
| 1-367 | Me | 3-[(4-Me-Pipra)-$(CH_2)_3$-O-$(CH_2)_3$]-Pip |
| 1-368 | Me | 3-[(4-Me-Pipra)-$(CH_2)_2$-S-$CH_2$]-Pip |
| 1-369 | Me | 3-(Pyrld-CO-$CH_2$-O-$CH_2$)-Pip |
| 1-370 | Me | 3-[Pyrld-CO-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-371 | Me | 3-[Pyrld-CO-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-372 | Me | 3-(Mor-CO-$CH_2$-O-$CH_2$)-Pip |
| 1-373 | Me | 3-[Mor-CO-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-374 | Me | 3-[Mor-CO-$CH_2$-O-$(CH_2)_3$]-Pip |

| | | |
|---|---|---|
| 1-375 | Me | 3-(Pipo-CO-$CH_2$-O-$CH_2$)-Pip |
| 1-376 | Me | 3-[Pipo-CO-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-377 | Me | 3-[Pipo-CO-$CH_2$-O-$(CH_2)_3$]-Pip |
| 1-378 | Me | 3-[(4-Me-Pipra)-CO-$CH_2$-O-$CH_2$]-Pip |
| 1-379 | Me | 3-[(4-Me-Pipra)-$CH_2$-O-$(CH_2)_2$]-Pip |
| 1-380 | Me | 3-[(4-Me-Pipra)-$CH_2$-O-$(CH_2)_3$]-Pip |

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Table 2

[Formula 6]




(I-1)

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Compound

| Number | $R^1$ | $R^a$ | $R^b$ |
|---|---|---|---|
| 2-1 | H | H | Me |
| 2-2 | H | H | Et |
| 2-3 | H | H | Pr |
| 2-4 | H | H | iPr |
| 2-5 | H | H | Bu |
| 2-6 | H | H | iBu |
| 2-7 | H | H | neoPn |
| 2-8 | H | H | cPn |
| 2-9 | H | H | cHx |
| 2-10 | H | H | cHep |

| | | | |
|---|---|---|---|
| 2-11 | H | H | Bn |
| 2-12 | H | H | Phet |
| 2-13 | H | H | Ph-$(CH_2)_3$ |
| 2-14 | H | H | cHx$CH_2$ |
| 2-15 | H | H | $MeOCH_2CH_2$ |
| 2-16 | H | H | $EtOCH_2CH_2$ |
| 2-17 | H | Me | Me |
| 2-18 | H | Me | Et |
| 2-19 | H | Me | Pr |
| 2-20 | H | Me | iPr |
| 2-21 | H | Me | Bu |
| 2-22 | H | Me | iBu |
| 2-23 | H | Me | neoPn |
| 2-24 | H | Me | cPn |
| 2-25 | H | Me | cHx |
| 2-26 | H | Me | cHep |
| 2-27 | H | Me | Bn |
| 2-28 | H | Me | Phet |
| 2-29 | H | Me | Ph-$(CH_2)_3$ |
| 2-30 | H | Me | cHx$CH_2$ |
| 2-31 | H | Me | $MeOCH_2CH_2$ |
| 2-32 | H | Me | $EtOCH_2CH_2$ |
| 2-33 | H | Et | Et |
| 2-34 | H | Et | Pr |
| 2-35 | H | Et | iPr |
| 2-36 | H | Et | Bu |
| 2-37 | H | Et | iBu |

| | | | |
|---|---|---|---|
| 2-38 | H | Et | neoPn |
| 2-39 | H | Et | cPn |
| 2-40 | H | Et | cHx |
| 2-41 | H | Et | cHep |
| 2-42 | H | Et | Bn |
| 2-43 | H | Et | Phet |
| 2-44 | H | Et | Ph-$(CH_2)_3$ |
| 2-45 | H | Et | cHx$CH_2$ |
| 2-46 | H | Et | Me$OCH_2CH_2$ |
| 2-47 | H | Et | Et$OCH_2CH_2$ |
| 2-48 | H | Pr | Pr |
| 2-49 | H | Pr | iPr |
| 2-50 | H | Pr | Bu |
| 2-51 | H | Pr | iBu |
| 2-52 | H | Pr | neoPn |
| 2-53 | H | Pr | cPn |
| 2-54 | H | Pr | cHx |
| 2-55 | H | Pr | cHep |
| 2-56 | H | Pr | Bn |
| 2-57 | H | Pr | Phet |
| 2-58 | H | Pr | Ph-$(CH_2)_3$ |
| 2-59 | H | Pr | cHx$CH_2$ |
| 2-60 | H | Pr | Me$OCH_2CH_2$ |
| 2-61 | H | Pr | Et$OCH_2CH_2$ |
| 2-62 | H | Me$OCH_2CH_2$ | iPr |
| 2-63 | H | Me$OCH_2CH_2$ | Bu |
| 2-64 | H | Me$OCH_2CH_2$ | iBu |

| | | | |
|---|---|---|---|
| 2-65 | H | $MeOCH_2CH_2$ | neoPn |
| 2-66 | H | $MeOCH_2CH_2$ | cPn |
| 2-67 | H | $MeOCH_2CH_2$ | cHx |
| 2-68 | H | $MeOCH_2CH_2$ | cHep |
| 2-69 | H | $MeOCH_2CH_2$ | Bn |
| 2-70 | H | $MeOCH_2CH_2$ | Phet |
| 2-71 | H | $MeOCH_2CH_2$ | $Ph\text{-}(CH_2)_3$ |
| 2-72 | H | $MeOCH_2CH_2$ | $cHxCH_2$ |
| 2-73 | H | $MeOCH_2CH_2$ | $MeOCH_2CH_2$ |
| 2-74 | H | $EtOCH_2CH_2$ | iPr |
| 2-75 | H | $EtOCH_2CH_2$ | Bu |
| 2-76 | H | $EtOCH_2CH_2$ | iBu |
| 2-77 | H | $EtOCH_2CH_2$ | neoPn |
| 2-78 | H | $EtOCH_2CH_2$ | cPn |
| 2-79 | H | $EtOCH_2CH_2$ | cHx |
| 2-80 | H | $EtOCH_2CH_2$ | cHep |
| 2-81 | H | $EtOCH_2CH_2$ | Bn |
| 2-82 | H | $EtOCH_2CH_2$ | Phet |
| 2-83 | H | $EtOCH_2CH_2$ | $Ph\text{-}(CH_2)_3$ |
| 2-84 | H | $EtOCH_2CH_2$ | $cHxCH_2$ |
| 2-85 | H | $EtOCH_2CH_2$ | $EtOCH_2CH_2$ |
| 2-86 | Me | H | Me |
| 2-87 | Me | H | Et |
| 2-88 | Me | H | Pr |
| 2-89 | Me | H | iPr |
| 2-90 | Me | H | Bu |
| 2-91 | Me | H | iBu |

| | | | |
|---|---|---|---|
| 2-92 | Me | H | neoPn |
| 2-93 | Me | H | cPn |
| 2-94 | Me | H | cHx |
| 2-95 | Me | H | cHep |
| 2-96 | Me | H | Bn |
| 2-97 | Me | H | Phet |
| 2-98 | Me | H | Ph-$(CH_2)_3$ |
| 2-99 | Me | H | $cHxCH_2$ |
| 2-100 | Me | H | $MeOCH_2CH_2$ |
| 2-101 | Me | H | $EtOCH_2CH_2$ |
| 2-102 | Me | Me | Me |
| 2-103 | Me | Me | Et |
| 2-104 | Me | Me | Pr |
| 2-105 | Me | Me | iPr |
| 2-106 | Me | Me | Bu |
| 2-107 | Me | Me | iBu |
| 2-108 | Me | Me | neoPn |
| 2-109 | Me | Me | cPn |
| 2-110 | Me | Me | cHx |
| 2-111 | Me | Me | cHep |
| 2-112 | Me | Me | Bn |
| 2-113 | Me | Me | Phet |
| 2-114 | Me | Me | Ph-$(CH_2)_3$ |
| 2-115 | Me | Me | $cHxCH_2$ |
| 2-116 | Me | Me | $MeOCH_2CH_2$ |
| 2-117 | Me | Me | $EtOCH_2CH_2$ |
| 2-118 | Me | Et | Et |

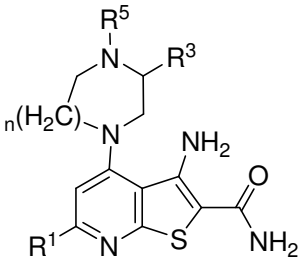
| | | | |
|---|---|---|---|
| 2-119 | Me | Et | Pr |
| 2-120 | Me | Et | iPr |
| 2-121 | Me | Et | Bu |
| 2-122 | Me | Et | iBu |
| 2-123 | Me | Et | neoPn |
| 2-124 | Me | Et | cPn |
| 2-125 | Me | Et | cHx |
| 2-126 | Me | Et | cHep |
| 2-127 | Me | Et | Bn |
| 2-128 | Me | Et | Phet |
| 2-129 | Me | Et | Ph-$(CH_2)_3$ |
| 2-130 | Me | Et | cHx$CH_2$ |
| 2-131 | Me | Et | Me$OCH_2CH_2$ |
| 2-132 | Me | Et | Et$OCH_2CH_2$ |
| 2-133 | Me | Pr | Pr |
| 2-134 | Me | Pr | iPr |
| 2-135 | Me | Pr | Bu |
| 2-136 | Me | Pr | iBu |
| 2-137 | Me | Pr | neoPn |
| 2-138 | Me | Pr | cPn |
| 2-139 | Me | Pr | cHx |
| 2-140 | Me | Pr | cHep |
| 2-141 | Me | Pr | Bn |
| 2-142 | Me | Pr | Phet |
| 2-143 | Me | Pr | Ph-$(CH_2)_3$ |
| 2-144 | Me | Pr | cHx$CH_2$ |
| 2-145 | Me | Pr | Me$OCH_2CH_2$ |

| | | | |
|---|---|---|---|
| 2-146 | Me | Pr | $EtOCH_2CH_2$ |
| 2-147 | Me | $MeOCH_2CH_2$ | iPr |
| 2-148 | Me | $MeOCH_2CH_2$ | Bu |
| 2-149 | Me | $MeOCH_2CH_2$ | iBu |
| 2-150 | Me | $MeOCH_2CH_2$ | neoPn |
| 2-151 | Me | $MeOCH_2CH_2$ | cPn |
| 2-152 | Me | $MeOCH_2CH_2$ | cHx |
| 2-153 | Me | $MeOCH_2CH_2$ | cHep |
| 2-154 | Me | $MeOCH_2CH_2$ | Bn |
| 2-155 | Me | $MeOCH_2CH_2$ | Phet |
| 2-156 | Me | $MeOCH_2CH_2$ | $Ph-(CH_2)_3$ |
| 2-157 | Me | $MeOCH_2CH_2$ | $cHxCH_2$ |
| 2-158 | Me | $MeOCH_2CH_2$ | $MeOCH_2CH_2$ |
| 2-159 | Me | $EtOCH_2CH_2$ | iPr |
| 2-160 | Me | $EtOCH_2CH_2$ | Bu |
| 2-161 | Me | $EtOCH_2CH_2$ | iBu |
| 2-162 | Me | $EtOCH_2CH_2$ | neoPn |
| 2-163 | Me | $EtOCH_2CH_2$ | cPn |
| 2-164 | Me | $EtOCH_2CH_2$ | cHx |
| 2-165 | Me | $EtOCH_2CH_2$ | cHep |
| 2-166 | Me | $EtOCH_2CH_2$ | Bn |
| 2-167 | Me | $EtOCH_2CH_2$ | Phet |
| 2-168 | Me | $EtOCH_2CH_2$ | $Ph-(CH_2)_3$ |
| 2-169 | Me | $EtOCH_2CH_2$ | $cHxCH_2$ |
| 2-170 | Me | $EtOCH_2CH_2$ | $EtOCH_2CH_2$ |

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Table 3

[Formula 7]



(I-2)

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Compound

| Number | $R^1$ | n | $R^3$ | $R^5$ |
|---|---|---|---|---|
| 3-1 | H | 1 | H | H |
| 3-2 | H | 1 | H | Me |
| 3-3 | H | 1 | H | Et |
| 3-4 | H | 1 | H | Pr |
| 3-5 | H | 1 | H | iPr |
| 3-6 | H | 1 | H | Bn |
| 3-7 | H | 1 | H | Bzhy |
| 3-8 | H | 1 | H | $PhCH=CHCH_2$ |
| 3-9 | H | 1 | H | Ph |
| 3-10 | H | 1 | H | 5-BzDioxo |
| 3-11 | H | 1 | H | 6-BzDioxa |
| 3-12 | H | 1 | H | 4-F-Ph |
| 3-13 | H | 1 | H | 3,4-diF-Ph |
| 3-14 | H | 1 | H | 3-Cl-4-F-Ph |
| 3-15 | H | 1 | H | 2-Cl-Ph |
| 3-16 | H | 1 | H | 3-Cl-Ph |

| | | | | |
|---|---|---|---|---|
| 3-17 | H | 1 | H | 4-Cl-Ph |
| 3-18 | H | 1 | H | 4-Br-Ph |
| 3-19 | H | 1 | H | 3-$NO_2$-Ph |
| 3-20 | H | 1 | H | 4-$NO_2$-Ph |
| 3-21 | H | 1 | H | 4-CN-Ph |
| 3-22 | H | 1 | H | 4-Ac-Ph |
| 3-23 | H | 1 | H | 4-EtCO-Ph |
| 3-24 | H | 1 | H | 4-(HOOC)-Ph |
| 3-25 | H | 1 | H | 4-(MeOOC)-Ph |
| 3-26 | H | 1 | H | 4-(EtOOC)-Ph |
| 3-27 | H | 1 | H | 4-$Me_2N$-Ph |
| 3-28 | H | 1 | H | 4-($H_2NCO$)-Ph |
| 3-29 | H | 1 | H | 4-(MeNHCO)-Ph |
| 3-30 | H | 1 | H | 4-($Me_2NCO$)-Ph |
| 3-31 | H | 1 | H | 4-($Et_2NCO$)-Ph |
| 3-32 | H | 1 | H | 2-Me-Ph |
| 3-33 | H | 1 | H | 3-Me-Ph |
| 3-34 | H | 1 | H | 4-Me-Ph |
| 3-35 | H | 1 | H | 4-Et-Ph |
| 3-36 | H | 1 | H | 4-Pr-Ph |
| 3-37 | H | 1 | H | 4-iPr-Ph |
| 3-38 | H | 1 | H | 4-tBu-Ph |
| 3-39 | H | 1 | H | 3,4-diMe-Ph |
| 3-40 | H | 1 | H | 3-F-4-Me-Ph |
| 3-41 | H | 1 | H | 4-F-3-Me-Ph |
| 3-42 | H | 1 | H | 3-$NO_2$-4-Me-Ph |
| 3-43 | H | 1 | H | 3-$CF_3$-Ph |

| | | | | |
|---|---|---|---|---|
| 3-44 | H | 1 | H | 4-$CF_3$-Ph |
| 3-45 | H | 1 | H | 2-MeO-Ph |
| 3-46 | H | 1 | H | 3-MeO-Ph |
| 3-47 | H | 1 | H | 4-MeO-Ph |
| 3-48 | H | 1 | H | 3,4-diMeO-Ph |
| 3-49 | H | 1 | H | 3,4,5-triMeO-Ph |
| 3-50 | H | 1 | H | 4-EtO-Ph |
| 3-51 | H | 1 | H | 4-PrO-Ph |
| 3-52 | H | 1 | H | 4-iPrO-Ph |
| 3-53 | H | 1 | H | 4-$CF_3$O-Ph |
| 3-54 | H | 1 | H | 4-MeS-Ph |
| 3-55 | H | 1 | H | 4-MeSO-Ph |
| 3-56 | H | 1 | H | 4-$MeSO_2$-Ph |
| 3-57 | H | 1 | H | 4-BnO-Ph |
| 3-58 | H | 1 | H | 2-Oxaz |
| 3-59 | H | 1 | H | 2-Thaz |
| 3-60 | H | 1 | H | 2-BzOxaz |
| 3-61 | H | 1 | H | 2-BzThaz |
| 3-62 | H | 1 | H | 2-Py |
| 3-63 | H | 1 | H | 3-Py |
| 3-64 | H | 1 | H | 4-Py |
| 3-65 | H | 1 | H | 5-Ac-2-Py |
| 3-66 | H | 1 | H | 5-Me-2-Py |
| 3-67 | H | 1 | H | 6-MeO-3-Py |
| 3-68 | H | 1 | H | 2,3,5,6-tetraF-4-Py |
| 3-69 | H | 1 | H | 2-Pym |
| 3-70 | H | 1 | H | 4-Qunz |

| | | | | |
|---|---|---|---|---|
| 3-71 | H | 1 | H | 6-Cl-3-Pydz |
| 3-72 | H | 1 | H | Ac |
| 3-73 | H | 1 | H | Ph-CO |
| 3-74 | H | 1 | H | $MeSO_2$ |
| 3-75 | H | 1 | H | tBuO-CO |
| 3-76 | Me | 1 | H | Ph |
| 3-77 | H | 1 | Me | 3-Me-Ph |
| 3-78 | H | 2 | H | H |
| 3-79 | H | 2 | H | Me |
| 3-80 | H | 2 | H | Et |
| 3-81 | H | 2 | H | Pr |
| 3-82 | H | 2 | H | iPr |
| 3-83 | H | 2 | H | Bn |
| 3-84 | H | 2 | H | Bzhy |
| 3-85 | H | 2 | H | $PhCH=CHCH_2$ |
| 3-86 | H | 2 | H | Ph |
| 3-87 | H | 2 | H | 5-BzDioxo |
| 3-88 | H | 2 | H | 6-BzDioxa |
| 3-89 | H | 2 | H | 4-F-Ph |
| 3-90 | H | 2 | H | 3,4-diF-Ph |
| 3-91 | H | 2 | H | 3-Cl-4-F-Ph |
| 3-92 | H | 2 | H | 2-Cl-Ph |
| 3-93 | H | 2 | H | 3-Cl-Ph |
| 3-94 | H | 2 | H | 4-Cl-Ph |
| 3-95 | H | 2 | H | 4-Br-Ph |
| 3-96 | H | 2 | H | 3-$NO_2$-Ph |
| 3-97 | H | 2 | H | 4-$NO_2$-Ph |

| | | | | |
|---|---|---|---|---|
| 3-98 | H | 2 | H | 4-CN-Ph |
| 3-99 | H | 2 | H | 4-Ac-Ph |
| 3-100 | H | 2 | H | 4-EtCO-Ph |
| 3-101 | H | 2 | H | 4-(HOOC)-Ph |
| 3-102 | H | 2 | H | 4-(MeOOC)-Ph |
| 3-103 | H | 2 | H | 4-(EtOOC)-Ph |
| 3-104 | H | 2 | H | 4-$Me_2N$-Ph |
| 3-105 | H | 2 | H | 4-($H_2NCO$)-Ph |
| 3-106 | H | 2 | H | 4-(MeNHCO)-Ph |
| 3-107 | H | 2 | H | 4-($Me_2NCO$)-Ph |
| 3-108 | H | 2 | H | 4-($Et_2NCO$)-Ph |
| 3-109 | H | 2 | H | 2-Me-Ph |
| 3-110 | H | 2 | H | 3-Me-Ph |
| 3-111 | H | 2 | H | 4-Me-Ph |
| 3-112 | H | 2 | H | 4-Et-Ph |
| 3-113 | H | 2 | H | 4-Pr-Ph |
| 3-114 | H | 2 | H | 4-iPr-Ph |
| 3-115 | H | 2 | H | 4-tBu-Ph |
| 3-116 | H | 2 | H | 3,4-diMe-Ph |
| 3-117 | H | 2 | H | 3-F-4-Me-Ph |
| 3-118 | H | 2 | H | 4-F-3-Me-Ph |
| 3-119 | H | 2 | H | 3-$NO_2$-4-Me-Ph |
| 3-120 | H | 2 | H | 3-$CF_3$-Ph |
| 3-121 | H | 2 | H | 4-$CF_3$-Ph |
| 3-122 | H | 2 | H | 2-MeO-Ph |
| 3-123 | H | 2 | H | 3-MeO-Ph |
| 3-124 | H | 2 | H | 4-MeO-Ph |

| | | | | |
|---|---|---|---|---|
| 3-125 | H | 2 | H | 3,4-diMeO-Ph |
| 3-126 | H | 2 | H | 3,4,5-triMeO-Ph |
| 3-127 | H | 2 | H | 4-EtO-Ph |
| 3-128 | H | 2 | H | 4-PrO-Ph |
| 3-129 | H | 2 | H | 4-iPrO-Ph |
| 3-130 | H | 2 | H | 4-$CF_3O$-Ph |
| 3-131 | H | 2 | H | 4-MeS-Ph |
| 3-132 | H | 2 | H | 4-MeSO-Ph |
| 3-133 | H | 2 | H | 4-$MeSO_2$-Ph |
| 3-134 | H | 2 | H | 4-BnO-Ph |
| 3-135 | H | 2 | H | 2-Oxaz |
| 3-136 | H | 2 | H | 2-Thaz |
| 3-137 | H | 2 | H | 2-BzOxaz |
| 3-138 | H | 2 | H | 2-BzThaz |
| 3-139 | H | 2 | H | 2-Py |
| 3-140 | H | 2 | H | 3-Py |
| 3-141 | H | 2 | H | 4-Py |
| 3-142 | H | 2 | H | 5-Ac-2-Py |
| 3-143 | H | 2 | H | 5-Me-2-Py |
| 3-144 | H | 2 | H | 6-MeO-3-Py |
| 3-145 | H | 2 | H | 2,3,5,6-tetraF-4-Py |
| 3-146 | H | 2 | H | 2-Pym |
| 3-147 | H | 2 | H | 4-Qunz |
| 3-148 | H | 2 | H | 6-Cl-3-Pydz |
| 3-149 | H | 2 | H | Ac |
| 3-150 | H | 2 | H | Ph-CO |
| 3-151 | H | 2 | H | $MeSO_2$ |

| | | | | |
|---|---|---|---|---|
| 3-152 | H | 2 | H | tBuO-CO |
| 3-153 | Me | 2 | H | H |
| 3-154 | Me | 2 | H | Me |
| 3-155 | Me | 2 | H | Et |
| 3-156 | Me | 2 | H | Pr |
| 3-157 | Me | 2 | H | iPr |
| 3-158 | Me | 2 | H | Bn |
| 3-159 | Me | 2 | H | Bzhy |
| 3-160 | Me | 2 | H | $PhCH=CHCH_2$ |
| 3-161 | Me | 2 | H | Ph |
| 3-162 | Me | 2 | H | 5-BzDioxo |
| 3-163 | Me | 2 | H | 6-BzDioxa |
| 3-164 | Me | 2 | H | 4-F-Ph |
| 3-165 | Me | 2 | H | 3,4-diF-Ph |
| 3-166 | Me | 2 | H | 3-Cl-4-F-Ph |
| 3-167 | Me | 2 | H | 2-Cl-Ph |
| 3-168 | Me | 2 | H | 3-Cl-Ph |
| 3-169 | Me | 2 | H | 4-Cl-Ph |
| 3-170 | Me | 2 | H | 4-Br-Ph |
| 3-171 | Me | 2 | H | $3\text{-}NO_2\text{-}Ph$ |
| 3-172 | Me | 2 | H | $4\text{-}NO_2\text{-}Ph$ |
| 3-173 | Me | 2 | H | 4-CN-Ph |
| 3-174 | Me | 2 | H | 4-Ac-Ph |
| 3-175 | Me | 2 | H | 4-EtCO-Ph |
| 3-176 | Me | 2 | H | 4-(HOOC)-Ph |
| 3-177 | Me | 2 | H | 4-(MeOOC)-Ph |
| 3-178 | Me | 2 | H | 4-(EtOOC)-Ph |

| | | | | |
|---|---|---|---|---|
| 3-179 | Me | 2 | H | 4-$Me_2N$-Ph |
| 3-180 | Me | 2 | H | 4-($H_2NCO$)-Ph |
| 3-181 | Me | 2 | H | 4-(MeNHCO)-Ph |
| 3-182 | Me | 2 | H | 4-($Me_2NCO$)-Ph |
| 3-183 | Me | 2 | H | 4-($Et_2NCO$)-Ph |
| 3-184 | Me | 2 | H | 2-Me-Ph |
| 3-185 | Me | 2 | H | 3-Me-Ph |
| 3-186 | Me | 2 | H | 4-Me-Ph |
| 3-187 | Me | 2 | H | 4-Et-Ph |
| 3-188 | Me | 2 | H | 4-Pr-Ph |
| 3-189 | Me | 2 | H | 4-iPr-Ph |
| 3-190 | Me | 2 | H | 4-tBu-Ph |
| 3-191 | Me | 2 | H | 3,4-diMe-Ph |
| 3-192 | Me | 2 | H | 3-F-4-Me-Ph |
| 3-193 | Me | 2 | H | 4-F-3-Me-Ph |
| 3-194 | Me | 2 | H | 3-$NO_2$-4-Me-Ph |
| 3-195 | Me | 2 | H | 3-$CF_3$-Ph |
| 3-196 | Me | 2 | H | 4-$CF_3$-Ph |
| 3-197 | Me | 2 | H | 2-MeO-Ph |
| 3-198 | Me | 2 | H | 3-MeO-Ph |
| 3-199 | Me | 2 | H | 4-MeO-Ph |
| 3-200 | Me | 2 | H | 3,4-diMeO-Ph |
| 3-201 | Me | 2 | H | 3,4,5-triMeO-Ph |
| 3-202 | Me | 2 | H | 4-EtO-Ph |
| 3-203 | Me | 2 | H | 4-PrO-Ph |
| 3-204 | Me | 2 | H | 4-iPrO-Ph |
| 3-205 | Me | 2 | H | 4-$CF_3O$-Ph |

| | | | | |
|---|---|---|---|---|
| 3-206 | Me | 2 | H | 4-MeS-Ph |
| 3-207 | Me | 2 | H | 4-MeSO-Ph |
| 3-208 | Me | 2 | H | 4-$MeSO_2$-Ph |
| 3-209 | Me | 2 | H | 4-BnO-Ph |
| 3-210 | Me | 2 | H | 2-Oxaz |
| 3-211 | Me | 2 | H | 2-Thaz |
| 3-212 | Me | 2 | H | 2-BzOxaz |
| 3-213 | Me | 2 | H | 2-BzThaz |
| 3-214 | Me | 2 | H | 2-Py |
| 3-215 | Me | 2 | H | 3-Py |
| 3-216 | Me | 2 | H | 4-Py |
| 3-217 | Me | 2 | H | 5-Ac-2-Py |
| 3-218 | Me | 2 | H | 5-Me-2-Py |
| 3-219 | Me | 2 | H | 6-MeO-3-Py |
| 3-220 | Me | 2 | H | 2,3,5,6-tetraF-4-Py |
| 3-221 | Me | 2 | H | 2-Pym |
| 3-222 | Me | 2 | H | 4-Qunz |
| 3-223 | Me | 2 | H | 6-Cl-3-Pydz |
| 3-224 | Me | 2 | H | Ac |
| 3-225 | Me | 2 | H | Ph-CO |
| 3-226 | Me | 2 | H | $MeSO_2$ |
| 3-227 | Me | 2 | H | tBuO-CO |
| 3-228 | H | 2 | Me | H |
| 3-229 | H | 2 | Me | Me |
| 3-230 | H | 2 | Me | Et |
| 3-231 | H | 2 | Me | Pr |
| 3-232 | H | 2 | Me | iPr |

| | | | | |
|---|---|---|---|---|
| 3-233 | H | 2 | Me | Bn |
| 3-234 | H | 2 | Me | Bzhy |
| 3-235 | H | 2 | Me | $PhCH=CHCH_2$ |
| 3-236 | H | 2 | Me | Ph |
| 3-237 | H | 2 | Me | 5-BzDioxo |
| 3-238 | H | 2 | Me | 6-BzDioxa |
| 3-239 | H | 2 | Me | 4-F-Ph |
| 3-240 | H | 2 | Me | 3,4-diF-Ph |
| 3-241 | H | 2 | Me | 3-Cl-4-F-Ph |
| 3-242 | H | 2 | Me | 2-Cl-Ph |
| 3-243 | H | 2 | Me | 3-Cl-Ph |
| 3-244 | H | 2 | Me | 4-Cl-Ph |
| 3-245 | H | 2 | Me | 4-Br-Ph |
| 3-246 | H | 2 | Me | $3\text{-}NO_2\text{-}Ph$ |
| 3-247 | H | 2 | Me | $4\text{-}NO_2\text{-}Ph$ |
| 3-248 | H | 2 | Me | 4-CN-Ph |
| 3-249 | H | 2 | Me | 4-Ac-Ph |
| 3-250 | H | 2 | Me | 4-EtCO-Ph |
| 3-251 | H | 2 | Me | 4-(HOOC)-Ph |
| 3-252 | H | 2 | Me | 4-(MeOOC)-Ph |
| 3-253 | H | 2 | Me | 4-(EtOOC)-Ph |
| 3-254 | H | 2 | Me | $4\text{-}Me_2N\text{-}Ph$ |
| 3-255 | H | 2 | Me | $4\text{-}(H_2NCO)\text{-}Ph$ |
| 3-256 | H | 2 | Me | 4-(MeNHCO)-Ph |
| 3-257 | H | 2 | Me | $4\text{-}(Me_2NCO)\text{-}Ph$ |
| 3-258 | H | 2 | Me | $4\text{-}(Et_2NCO)\text{-}Ph$ |
| 3-259 | H | 2 | Me | 2-Me-Ph |

| | | | | |
|---|---|---|---|---|
| 3-260 | H | 2 | Me | 3-Me-Ph |
| 3-261 | H | 2 | Me | 4-Me-Ph |
| 3-262 | H | 2 | Me | 4-Et-Ph |
| 3-263 | H | 2 | Me | 4-Pr-Ph |
| 3-264 | H | 2 | Me | 4-iPr-Ph |
| 3-265 | H | 2 | Me | 4-tBu-Ph |
| 3-266 | H | 2 | Me | 3,4-diMe-Ph |
| 3-267 | H | 2 | Me | 3-F-4-Me-Ph |
| 3-268 | H | 2 | Me | 4-F-3-Me-Ph |
| 3-269 | H | 2 | Me | 3-$NO_2$-4-Me-Ph |
| 3-270 | H | 2 | Me | 3-$CF_3$-Ph |
| 3-271 | H | 2 | Me | 4-$CF_3$-Ph |
| 3-272 | H | 2 | Me | 2-MeO-Ph |
| 3-273 | H | 2 | Me | 3-MeO-Ph |
| 3-274 | H | 2 | Me | 4-MeO-Ph |
| 3-275 | H | 2 | Me | 3,4-diMeO-Ph |
| 3-276 | H | 2 | Me | 3,4,5-triMeO-Ph |
| 3-277 | H | 2 | Me | 4-EtO-Ph |
| 3-278 | H | 2 | Me | 4-PrO-Ph |
| 3-279 | H | 2 | Me | 4-iPrO-Ph |
| 3-280 | H | 2 | Me | 4-$CF_3$O-Ph |
| 3-281 | H | 2 | Me | 4-MeS-Ph |
| 3-282 | H | 2 | Me | 4-MeSO-Ph |
| 3-283 | H | 2 | Me | 4-$MeSO_2$-Ph |
| 3-284 | H | 2 | Me | 4-BnO-Ph |
| 3-285 | H | 2 | Me | 2-Oxaz |
| 3-286 | H | 2 | Me | 2-Thaz |

| | | | | |
|---|---|---|---|---|
| 3-287 | H | 2 | Me | 2-BzOxaz |
| 3-288 | H | 2 | Me | 2-BzThaz |
| 3-289 | H | 2 | Me | 2-Py |
| 3-290 | H | 2 | Me | 3-Py |
| 3-291 | H | 2 | Me | 4-Py |
| 3-292 | H | 2 | Me | 5-Ac-2-Py |
| 3-293 | H | 2 | Me | 5-Me-2-Py |
| 3-294 | H | 2 | Me | 6-MeO-3-Py |
| 3-295 | H | 2 | Me | 2,3,5,6-tetraF-4-Py |
| 3-296 | H | 2 | Me | 2-Pym |
| 3-297 | H | 2 | Me | 4-Qunz |
| 3-298 | H | 2 | Me | 6-Cl-3-Pydz |
| 3-299 | H | 2 | Me | Ac |
| 3-300 | H | 2 | Me | Ph-CO |
| 3-301 | H | 2 | Me | $MeSO_2$ |
| 3-302 | H | 2 | Me | tBuO-CO |
| 3-303 | Me | 2 | Me | H |
| 3-304 | Me | 2 | Me | Me |
| 3-305 | Me | 2 | Me | Et |
| 3-306 | Me | 2 | Me | Pr |
| 3-307 | Me | 2 | Me | iPr |
| 3-308 | Me | 2 | Me | Bn |
| 3-309 | Me | 2 | Me | Bzhy |
| 3-310 | Me | 2 | Me | $PhCH=CHCH_2$ |
| 3-311 | Me | 2 | Me | Ph |
| 3-312 | Me | 2 | Me | 5-BzDioxo |
| 3-313 | Me | 2 | Me | 6-BzDioxa |

| | | | | |
|---|---|---|---|---|
| 3-314 | Me | 2 | Me | 4-F-Ph |
| 3-315 | Me | 2 | Me | 3,4-diF-Ph |
| 3-316 | Me | 2 | Me | 3-Cl-4-F-Ph |
| 3-317 | Me | 2 | Me | 2-Cl-Ph |
| 3-318 | Me | 2 | Me | 3-Cl-Ph |
| 3-319 | Me | 2 | Me | 4-Cl-Ph |
| 3-320 | Me | 2 | Me | 4-Br-Ph |
| 3-321 | Me | 2 | Me | 3-$NO_2$-Ph |
| 3-322 | Me | 2 | Me | 4-$NO_2$-Ph |
| 3-323 | Me | 2 | Me | 4-CN-Ph |
| 3-324 | Me | 2 | Me | 4-Ac-Ph |
| 3-325 | Me | 2 | Me | 4-EtCO-Ph |
| 3-326 | Me | 2 | Me | 4-(HOOC)-Ph |
| 3-327 | Me | 2 | Me | 4-(MeOOC)-Ph |
| 3-328 | Me | 2 | Me | 4-(EtOOC)-Ph |
| 3-329 | Me | 2 | Me | 4-$Me_2N$-Ph |
| 3-330 | Me | 2 | Me | 4-($H_2NCO$)-Ph |
| 3-331 | Me | 2 | Me | 4-(MeNHCO)-Ph |
| 3-332 | Me | 2 | Me | 4-($Me_2NCO$)-Ph |
| 3-333 | Me | 2 | Me | 4-($Et_2NCO$)-Ph |
| 3-334 | Me | 2 | Me | 2-Me-Ph |
| 3-335 | Me | 2 | Me | 3-Me-Ph |
| 3-336 | Me | 2 | Me | 4-Me-Ph |
| 3-337 | Me | 2 | Me | 4-Et-Ph |
| 3-338 | Me | 2 | Me | 4-Pr-Ph |
| 3-339 | Me | 2 | Me | 4-iPr-Ph |
| 3-340 | Me | 2 | Me | 4-tBu-Ph |

| | | | | |
|---|---|---|---|---|
| 3-341 | Me | 2 | Me | 3,4-diMe-Ph |
| 3-342 | Me | 2 | Me | 3-F-4-Me-Ph |
| 3-343 | Me | 2 | Me | 4-F-3-Me-Ph |
| 3-344 | Me | 2 | Me | 3-$NO_2$-4-Me-Ph |
| 3-345 | Me | 2 | Me | 3-$CF_3$-Ph |
| 3-346 | Me | 2 | Me | 4-$CF_3$-Ph |
| 3-347 | Me | 2 | Me | 2-MeO-Ph |
| 3-348 | Me | 2 | Me | 3-MeO-Ph |
| 3-349 | Me | 2 | Me | 4-MeO-Ph |
| 3-350 | Me | 2 | Me | 3,4-diMeO-Ph |
| 3-351 | Me | 2 | Me | 3,4,5-triMeO-Ph |
| 3-352 | Me | 2 | Me | 4-EtO-Ph |
| 3-353 | Me | 2 | Me | 4-PrO-Ph |
| 3-354 | Me | 2 | Me | 4-iPrO-Ph |
| 3-355 | Me | 2 | Me | 4-$CF_3$O-Ph |
| 3-356 | Me | 2 | Me | 4-MeS-Ph |
| 3-357 | Me | 2 | Me | 4-MeSO-Ph |
| 3-358 | Me | 2 | Me | 4-$MeSO_2$-Ph |
| 3-359 | Me | 2 | Me | 4-BnO-Ph |
| 3-360 | Me | 2 | Me | 2-Oxaz |
| 3-361 | Me | 2 | Me | 2-Thaz |
| 3-362 | Me | 2 | Me | 2-BzOxaz |
| 3-363 | Me | 2 | Me | 2-BzThaz |
| 3-364 | Me | 2 | Me | 2-Py |
| 3-365 | Me | 2 | Me | 3-Py |
| 3-366 | Me | 2 | Me | 4-Py |
| 3-367 | Me | 2 | Me | 5-Ac-2-Py |

| | | | | |
|---|---|---|---|---|
| 3-368 | Me | 2 | Me | 5-Me-2-Py |
| 3-369 | Me | 2 | Me | 6-MeO-3-Py |
| 3-370 | Me | 2 | Me | 2,3,5,6-tetraF-4-Py |
| 3-371 | Me | 2 | Me | 2-Pym |
| 3-372 | Me | 2 | Me | 4-Qunz |
| 3-373 | Me | 2 | Me | 6-Cl-3-Pydz |
| 3-374 | Me | 2 | Me | Ac |
| 3-375 | Me | 2 | Me | Ph-CO |
| 3-376 | Me | 2 | Me | $MeSO_2$ |
| 3-377 | Me | 2 | Me | tBuO-CO |
| 3-378 | H | 1 | H | 4-(MeO-$CH_2$)-Ph |
| 3-379 | H | 1 | H | 3-(MeO-$CH_2$)-Ph |
| 3-380 | H | 1 | H | 4-[MeO-$(CH_2)_2$]-Ph |
| 3-381 | H | 1 | H | 3-[MeO-$(CH_2)_2$]-Ph |
| 3-382 | H | 1 | H | 4-[MeO-$(CH_2)_3$]-Ph |
| 3-383 | H | 1 | H | 3-[MeO-$(CH_2)_3$]-Ph |
| 3-384 | H | 1 | H | 4-(EtO-$CH_2$)-Ph |
| 3-385 | H | 1 | H | 3-(EtO-$CH_2$)-Ph |
| 3-386 | H | 1 | H | 4-[EtO-$(CH_2)_2$]-Ph |
| 3-387 | H | 1 | H | 3-[EtO-$(CH_2)_2$]-Ph |
| 3-388 | H | 1 | H | 4-[EtO-$(CH_2)_3$]-Ph |
| 3-389 | H | 1 | H | 3-[EtO-$(CH_2)_3$]-Ph |
| 3-390 | H | 1 | H | 4-cPrO-Ph |
| 3-391 | H | 1 | H | 3-cPrO-Ph |
| 3-392 | H | 1 | H | 4-(cPrO-$CH_2$)-Ph |
| 3-393 | H | 1 | H | 3-(cPrO-$CH_2$)-Ph |
| 3-394 | H | 1 | H | 4-[cPrO-$(CH_2)_2$]-Ph |

| | | | | |
|---|---|---|---|---|
| 3-395 | H | 1 | H | 3-[cPrO-$(CH_2)_2$]-Ph |
| 3-396 | H | 1 | H | 4-[cPrO-$(CH_2)_3$]-Ph |
| 3-397 | H | 1 | H | 3-[cPrO-$(CH_2)_3$]-Ph |
| 3-398 | H | 1 | H | 4-$CHF_2O$-Ph |
| 3-399 | H | 1 | H | 3-$CHF_2O$-Ph |
| 3-400 | H | 1 | H | 4-($CHF_2O$-$CH_2$)-Ph |
| 3-401 | H | 1 | H | 3-($CHF_2O$-$CH_2$)-Ph |
| 3-402 | H | 1 | H | 4-[$CHF_2O$-$(CH_2)_2$]-Ph |
| 3-403 | H | 1 | H | 3-[$CHF_2O$-$(CH_2)_2$]-Ph |
| 3-404 | H | 1 | H | 4-[$CHF_2O$-$(CH_2)_3$]-Ph |
| 3-405 | H | 1 | H | 3-[$CHF_2O$-$(CH_2)_3$]-Ph |
| 3-406 | H | 1 | H | 3-($H_2NCO$)-Ph |
| 3-407 | H | 1 | H | 4-($H_2NCO$-$CH_2$)-Ph |
| 3-408 | H | 1 | H | 3-($H_2NCO$-$CH_2$)-Ph |
| 3-409 | H | 1 | H | 4-[$H_2NCO$-$(CH_2)_2$]-Ph |
| 3-410 | H | 1 | H | 3-[$H_2NCO$-$(CH_2)_2$]-Ph |
| 3-411 | H | 1 | H | 3-(MeNHCO)-Ph |
| 3-412 | H | 1 | H | 4-(MeNHCO-$CH_2$)-Ph |
| 3-413 | H | 1 | H | 3-(MeNHCO-$CH_2$)-Ph |
| 3-414 | H | 1 | H | 4-[MeNHCO-$(CH_2)_2$]-Ph |
| 3-415 | H | 1 | H | 3-[MeNHCO-$(CH_2)_2$]-Ph |
| 3-416 | H | 1 | H | 4-(iPrNHCO)-Ph |
| 3-417 | H | 1 | H | 3-(iPrNHCO)-Ph |
| 3-418 | H | 1 | H | 4-(iPrNHCO-$CH_2$)-Ph |
| 3-419 | H | 1 | H | 3-(iPrNHCO-$CH_2$)-Ph |
| 3-420 | H | 1 | H | 4-[iPrNHCO-$(CH_2)_2$]-Ph |
| 3-421 | H | 1 | H | 3-[iPrNHCO-$(CH_2)_2$]-Ph |

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|---|---|---|---|---|
| 3-422 | H | 1 | H | 4-(EtNMeCO)-Ph |
| 3-423 | H | 1 | H | 3-(EtNMeCO)-Ph |
| 3-424 | H | 1 | H | 4-(EtNMeCO-$CH_2$)-Ph |
| 3-425 | H | 1 | H | 3-(EtNMeCO-$CH_2$)-Ph |
| 3-426 | H | 1 | H | 4-[EtNMeCO-$(CH_2)_2$]-Ph |
| 3-427 | H | 1 | H | 3-[EtNMeCO-$(CH_2)_2$]-Ph |
| 3-428 | H | 1 | H | 3-($Me_2$NCO)-Ph |
| 3-429 | H | 1 | H | 4-($Me_2$NCO-$CH_2$)-Ph |
| 3-430 | H | 1 | H | 3-($Me_2$NCO-$CH_2$)-Ph |
| 3-431 | H | 1 | H | 4-[$Me_2$NCO-$(CH_2)_2$]-Ph |
| 3-432 | H | 1 | H | 3-[$Me_2$NCO-$(CH_2)_2$]-Ph |
| 3-433 | H | 1 | H | 3-($Et_2$NCO)-Ph |
| 3-434 | H | 1 | H | 4-($Et_2$NCO-$CH_2$)-Ph |
| 3-435 | H | 1 | H | 3-($Et_2$NCO-$CH_2$)-Ph |
| 3-436 | H | 1 | H | 4-[$Et_2$NCO-$(CH_2)_2$]-Ph |
| 3-437 | H | 1 | H | 3-[$Et_2$NCO-$(CH_2)_2$]-Ph |
| 3-438 | H | 1 | H | 4-[(MeO)NMeCO]-Ph |
| 3-439 | H | 1 | H | 3-[(MeO)NMeCO]-Ph |
| 3-440 | H | 1 | H | 4-[(MeO)NMeCO-$CH_2$]-Ph |
| 3-441 | H | 1 | H | 3-[(MeO)NMeCO-$CH_2$]-Ph |
| 3-442 | H | 1 | H | 4-[(MeO)NMeCO-$(CH_2)_2$]-Ph |
| 3-443 | H | 1 | H | 3-[(MeO)NMeCO-$(CH_2)_2$]-Ph |
| 3-444 | H | 1 | H | 4-(Aze-CO)-Ph |
| 3-445 | H | 1 | H | 3-(Aze-CO)-Ph |
| 3-446 | H | 1 | H | 4-(Aze-CO-$CH_2$)-Ph |
| 3-447 | H | 1 | H | 3-(Aze-CO-$CH_2$)-Ph |
| 3-448 | H | 1 | H | 4-[Aze-CO-$(CH_2)_2$]-Ph |

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|---|---|---|---|---|
| 3-449 | H | 1 | H | 3-[Aze-CO-$(CH_2)_2$]-Ph |
| 3-450 | H | 1 | H | 4-[(3-HO-1-Aze)-CO]-Ph |
| 3-451 | H | 1 | H | 3-[(3-HO-1-Aze)-CO]-Ph |
| 3-452 | H | 1 | H | 4-[(3-HO-Aze)-CO-$CH_2$]-Ph |
| 3-453 | H | 1 | H | 3-[(3-HO-Aze)-CO-$CH_2$]-Ph |
| 3-454 | H | 1 | H | 4-[(3-HO-Aze)-CO-$(CH_2)_2$]-Ph |
| 3-455 | H | 1 | H | 3-[(3-HO-Aze)-CO-$(CH_2)_2$]-Ph |
| 3-456 | H | 1 | H | 4-(Pyrld-CO)-Ph |
| 3-457 | H | 1 | H | 3-(Pyrld-CO)-Ph |
| 3-458 | H | 1 | H | 4-(Pyrld-CO-$CH_2$)-Ph |
| 3-459 | H | 1 | H | 3-(Pyrld-CO-$CH_2$)-Ph |
| 3-460 | H | 1 | H | 4-[Pyrld-CO-$(CH_2)_2$]-Ph |
| 3-461 | H | 1 | H | 3-[Pyrld-CO-$(CH_2)_2$]-Ph |
| 3-462 | H | 1 | H | 4-(Pipo-CO)-Ph |
| 3-463 | H | 1 | H | 3-(Pipo-CO)-Ph |
| 3-464 | H | 1 | H | 4-(Pipo-CO-$CH_2$)-Ph |
| 3-465 | H | 1 | H | 3-(Pipo-CO-$CH_2$)-Ph |
| 3-466 | H | 1 | H | 4-[Pipo-CO-$(CH_2)_2$]-Ph |
| 3-467 | H | 1 | H | 3-[Pipo-CO-$(CH_2)_2$]-Ph |
| 3-468 | H | 1 | H | 4-[(4-Me-Pipra)-CO]-Ph |
| 3-469 | H | 1 | H | 3-[(4-Me-Pipra)-CO]-Ph |
| 3-470 | H | 1 | H | 4-[(4-Me-Pipra)-CO-$CH_2$]-Ph |
| 3-471 | H | 1 | H | 3-[(4-Me-Pipra)-CO-$CH_2$]-Ph |
| 3-472 | H | 1 | H | 4-[(4-Me-Pipra)-CO-$(CH_2)_2$]-Ph |
| 3-473 | H | 1 | H | 3-[(4-Me-Pipra)-CO-$(CH_2)_2$]-Ph |
| 3-474 | H | 1 | H | 4-(Mor-CO)-Ph |
| 3-475 | H | 1 | H | 3-(Mor-CO)-Ph |

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|---|---|---|---|---|
| 3-476 | H | 1 | H | 4-(Mor-CO-$CH_2$)-Ph |
| 3-477 | H | 1 | H | 3-(Mor-CO-$CH_2$)-Ph |
| 3-478 | H | 1 | H | 4-[Mor-CO-$(CH_2)_2$]-Ph |
| 3-479 | H | 1 | H | 3-[Mor-CO-$(CH_2)_2$]-Ph |
| 3-480 | H | 1 | H | 3-$Me_2N$-Ph |
| 3-481 | H | 1 | H | 4-($Me_2N$-$CH_2$)-Ph |
| 3-482 | H | 1 | H | 3-($Me_2N$-$CH_2$)-Ph |
| 3-483 | H | 1 | H | 4-[$Me_2N$-$(CH_2)_2$]-Ph |
| 3-484 | H | 1 | H | 3-[$Me_2N$-$(CH_2)_2$]-Ph |
| 3-485 | H | 1 | H | 4-[$Me_2N$-$(CH_2)_3$]-Ph |
| 3-486 | H | 1 | H | 3-[$Me_2N$-$(CH_2)_3$]-Ph |
| 3-487 | H | 1 | H | 4-Mor-Ph |
| 3-488 | H | 1 | H | 3-Mor-Ph |
| 3-489 | H | 1 | H | 4-(Mor-$CH_2$)-Ph |
| 3-490 | H | 1 | H | 3-(Mor-$CH_2$)-Ph |
| 3-491 | H | 1 | H | 4-[Mor-$(CH_2)_2$]-Ph |
| 3-492 | H | 1 | H | 3-[Mor-$(CH_2)_2$]-Ph |
| 3-493 | H | 1 | H | 4-[Mor-$(CH_2)_3$]-Ph |
| 3-494 | H | 1 | H | 3-[Mor-$(CH_2)_3$]-Ph |
| 3-495 | H | 1 | H | 4-Pipo-Ph |
| 3-496 | H | 1 | H | 3-Pipo-Ph |
| 3-497 | H | 1 | H | 4-(Pipo-$CH_2$)-Ph |
| 3-498 | H | 1 | H | 3-(Pipo-$CH_2$)-Ph |
| 3-499 | H | 1 | H | 4-[Pipo-$(CH_2)_2$]-Ph |
| 3-500 | H | 1 | H | 3-[Pipo-$(CH_2)_2$]-Ph |
| 3-501 | H | 1 | H | 4-[Pipo-$(CH_2)_3$]-Ph |
| 3-502 | H | 1 | H | 3-[Pipo-$(CH_2)_3$]-Ph |

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|---|---|---|---|---|
| 3-503 | H | 1 | H | 4-HO-Ph |
| 3-504 | H | 1 | H | 3-HO-Ph |
| 3-505 | H | 1 | H | 4-(HO-$CH_2$)-Ph |
| 3-506 | H | 1 | H | 3-(HO-$CH_2$)-Ph |
| 3-507 | H | 1 | H | 4-[HO-$(CH_2)_2$]-Ph |
| 3-508 | H | 1 | H | 3-[HO-$(CH_2)_2$]-Ph |
| 3-509 | H | 1 | H | 4-[HO-$(CH_2)_3$]-Ph |
| 3-510 | H | 1 | H | 3-[HO-$(CH_2)_3$]-Ph |
| 3-511 | H | 1 | H | 4-[MeCH(OH)]-Ph |
| 3-512 | H | 1 | H | 3-[MeCH(OH)]-Ph |
| 3-513 | H | 1 | H | 4-[MeCH(OH)-$CH_2$]-Ph |
| 3-514 | H | 1 | H | 3-[MeCH(OH)-$CH_2$]-Ph |
| 3-515 | H | 1 | H | 4-[MeCH(OH)-$(CH_2)_2$]-Ph |
| 3-516 | H | 1 | H | 3-[MeCH(OH)-$(CH_2)_2$]-Ph |
| 3-517 | H | 1 | H | 3-CN-Ph |
| 3-518 | H | 1 | H | 4-(CN-$CH_2$)-Ph |
| 3-519 | H | 1 | H | 3-(CN-$CH_2$)-Ph |
| 3-520 | H | 1 | H | 4-[CN-$(CH_2)_2$]-Ph |
| 3-521 | H | 1 | H | 3-[CN-$(CH_2)_2$]-Ph |
| 3-522 | H | 1 | H | 3-Ac-Ph |
| 3-523 | H | 1 | H | 4-(Ac-$CH_2$)-Ph |
| 3-524 | H | 1 | H | 3-(Ac-$CH_2$)-Ph |
| 3-525 | H | 1 | H | 4-[Ac-$(CH_2)_2$]-Ph |
| 3-526 | H | 1 | H | 3-[Ac-$(CH_2)_2$]-Ph |
| 3-527 | H | 1 | H | 4-($CF_3$CO)-Ph |
| 3-528 | H | 1 | H | 4-(EtCO)-Ph |
| 3-529 | H | 1 | H | 3-(EtCO)-Ph |

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|---|---|---|---|---|
| 3-530 | H | 1 | H | 4-(EtCO-$CH_2$)-Ph |
| 3-531 | H | 1 | H | 3-(EtCO-$CH_2$)-Ph |
| 3-532 | H | 1 | H | 4-[EtCO-$(CH_2)_2$]-Ph |
| 3-533 | H | 1 | H | 3-[EtCO-$(CH_2)_2$]-Ph |
| 3-534 | H | 1 | H | 4-(iPrCO)-Ph |
| 3-535 | H | 1 | H | 4-(cBuCO)-Ph |
| 3-536 | H | 1 | H | 4-(cPrCO)-Ph |
| 3-537 | H | 1 | H | 4-(Ph-CO)-Ph |
| 3-538 | H | 1 | H | 4-Ac-3-MeO-Ph |
| 3-539 | H | 1 | H | 4-Ac-3-OH-Ph |
| 3-540 | H | 1 | H | 4-Ac-3-Cl-Ph |
| 3-541 | H | 1 | H | 4-[$CH_3C$(=N-OH)]-Ph |
| 3-542 | H | 1 | H | 3-[$CH_3C$(=N-OH)]-Ph |
| 3-543 | H | 1 | H | 4-[$CH_3C$(=N-OH)-$CH_2$]-Ph |
| 3-544 | H | 1 | H | 3-[$CH_3C$(=N-OH)-$CH_2$]-Ph |
| 3-545 | H | 1 | H | 4-[$CH_3C$(=N-OH)-$(CH_2)_2$]-Ph |
| 3-546 | H | 1 | H | 3-[$CH_3C$(=N-OH)-$(CH_2)_2$]-Ph |
| 3-547 | H | 1 | H | 4-[$CH_3C$(=N-OMe)]-Ph |
| 3-548 | H | 1 | H | 3-[$CH_3C$(=N-OMe)]-Ph |
| 3-549 | H | 1 | H | 4-[$CH_3C$(=N-OMe)-$CH_2$]-Ph |
| 3-550 | H | 1 | H | 3-[$CH_3C$(=N-OMe)-$CH_2$]-Ph |
| 3-551 | H | 1 | H | 4-[$CH_3C$(=N-OMe)-$(CH_2)_2$]-Ph |
| 3-552 | H | 1 | H | 3-[$CH_3C$(=N-OMe)-$(CH_2)_2$]-Ph |
| 3-553 | H | 1 | H | 4-($Me_2NSO_2$)-Ph |
| 3-554 | H | 1 | H | 4-[$(MeO)_2CH$]-Ph |
| 3-555 | H | 1 | H | 3-[$(MeO)_2CH$]-Ph |
| 3-556 | H | 1 | H | 4-[$(MeO)_2CH$-$CH_2$]-Ph |

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|---|---|---|---|---|
| 3-557 | H | 1 | H | 3-[$(MeO)_2CH$-$CH_2$]-Ph |
| 3-558 | H | 1 | H | 4-[$(MeO)_2CH$-$(CH_2)_2$]-Ph |
| 3-559 | H | 1 | H | 3-[$(MeO)_2CH$-$(CH_2)_2$]-Ph |
| 3-560 | H | 1 | H | 4-[$Me(MeO)_2C$]-Ph |
| 3-561 | H | 1 | H | 3-[$Me(MeO)_2C$]-Ph |
| 3-562 | H | 1 | H | 4-[$Me(MeO)_2C$-$CH_2$]-Ph |
| 3-563 | H | 1 | H | 3-[$Me(MeO)_2C$-$CH_2$]-Ph |
| 3-564 | H | 1 | H | 4-[$Me(MeO)_2C$-$(CH_2)_2$]-Ph |
| 3-565 | H | 1 | H | 3-[$Me(MeO)_2C$-$(CH_2)_2$]-Ph |
| 3-566 | H | 1 | H | 4-[$(EtO)_2CH$]-Ph |
| 3-567 | H | 1 | H | 3-[$(EtO)_2CH$]-Ph |
| 3-568 | H | 1 | H | 4-[$(EtO)_2CH$-$CH_2$]-Ph |
| 3-569 | H | 1 | H | 3-[$(EtO)_2CH$-$CH_2$]-Ph |
| 3-570 | H | 1 | H | 4-[$(EtO)_2CH$-$(CH_2)_2$]-Ph |
| 3-571 | H | 1 | H | 3-[$(EtO)_2CH$-$(CH_2)_2$]-Ph |
| 3-572 | H | 1 | H | 4-[$Me(EtO)_2C$]-Ph |
| 3-573 | H | 1 | H | 3-[$Me(EtO)_2C$]-Ph |
| 3-574 | H | 1 | H | 4-[$Me(EtO)_2C$-$CH_2$]-Ph |
| 3-575 | H | 1 | H | 3-[$Me(EtO)_2C$-$CH_2$]-Ph |
| 3-576 | H | 1 | H | 4-[$Me(EtO)_2C$-$(CH_2)_2$]-Ph |
| 3-577 | H | 1 | H | 3-[$Me(EtO)_2C$-$(CH_2)_2$]-Ph |
| 3-578 | H | 1 | H | 4-(2-Dioxo)-Ph |
| 3-579 | H | 1 | H | 3-(2-Dioxo)-Ph |
| 3-580 | H | 1 | H | 4-[(2-Dioxo)-$CH_2$]-Ph |
| 3-581 | H | 1 | H | 3-[(2-Dioxo)-$CH_2$]-Ph |
| 3-582 | H | 1 | H | 4-[(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-583 | H | 1 | H | 3-[(2-Dioxo)-$(CH_2)_2$]-Ph |

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| 3-584 | H | 1 | H | 4-[2-Me-(2-Dioxo)]-Ph |
| 3-585 | H | 1 | H | 3-[2-Me-(2-Dioxo)]-Ph |
| 3-586 | H | 1 | H | 4-[2-Me-(2-Dioxo)-$CH_2$]-Ph |
| 3-587 | H | 1 | H | 3-[2-Me-(2-Dioxo)-$CH_2$]-Ph |
| 3-588 | H | 1 | H | 4-[2-Me-(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-589 | H | 1 | H | 3-[2-Me-(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-590 | H | 1 | H | 4-(2-Dioxa)-Ph |
| 3-591 | H | 1 | H | 3-(2-Dioxa)-Ph |
| 3-592 | H | 1 | H | 4-[(2-Dioxa)-$CH_2$]-Ph |
| 3-593 | H | 1 | H | 3-[(2-Dioxa)-$CH_2$]-Ph |
| 3-594 | H | 1 | H | 4-[(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-595 | H | 1 | H | 3-[(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-596 | H | 1 | H | 4-[2-Me-(2-Dioxa)]-Ph |
| 3-597 | H | 1 | H | 3-[2-Me-(2-Dioxa)]-Ph |
| 3-598 | H | 1 | H | 4-[2-Me-(2-Dioxa)-$CH_2$]-Ph |
| 3-599 | H | 1 | H | 3-[2-Me-(2-Dioxa)-$CH_2$]-Ph |
| 3-600 | H | 1 | H | 4-[2-Me-(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-601 | H | 1 | H | 3-[2-Me-(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-602 | H | 1 | H | 2-Me-1-oxo-5-IIndn |
| 3-603 | H | 1 | H | 6-BzOxaz |
| 3-604 | H | 1 | H | 4-(HO-N=)-7-Chr |
| 3-605 | H | 1 | H | 3-Me-6-BzIox |
| 3-606 | H | 1 | H | 2-Me-6-BzOxaz |
| 3-607 | H | 1 | H | 2-Me-5-BzOxaz |
| 3-608 | H | 1 | H | 2,3-dihydro-5-BzFur |
| 3-609 | H | 1 | H | 6-Qui |
| 3-610 | H | 1 | H | 6-Iqui |

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| 3-611 | H | 1 | H | 3-(HO-N=)-2,3-dihydro-6-BzFur |
| 3-612 | H | 1 | H | 2-Me-6-BzThaz |
| 3-613 | H | 1 | H | 5-Ind |
| 3-614 | H | 1 | H | 4-Ac-2-Thaz |
| 3-615 | H | 1 | H | 5-Ac-2-Thi |
| 3-616 | H | 1 | H | 5-Ac-2-Fur |
| 3-617 | H | 1 | H | 5-$Me_2$NCO-2-Py |
| 3-618 | H | 1 | H | 5-($Me_2$NCO-$CH_2$)-2-Py |
| 3-619 | H | 1 | H | 5-[$Me_2$NCO-$(CH_2)_2$]-2-Py |
| 3-620 | H | 1 | H | 4-$Me_2$NCO-2-Thaz |
| 3-621 | H | 1 | H | 5-$Me_2$NCO-2-Thaz |
| 3-622 | H | 1 | H | 4-($Me_2$NCO-$CH_2$)-2-Thaz |
| 3-623 | H | 1 | H | 5-($Me_2$NCO-$CH_2$)-2-Thaz |
| 3-624 | H | 1 | H | 2-Thazn |
| 3-625 | H | 1 | H | 2-Oxazn |
| 3-626 | Me | 1 | H | 4-(MeO-$CH_2$)-Ph |
| 3-627 | Me | 1 | H | 3-(MeO-$CH_2$)-Ph |
| 3-628 | Me | 1 | H | 4-[MeO-$(CH_2)_2$]-Ph |
| 3-629 | Me | 1 | H | 3-[MeO-$(CH_2)_2$]-Ph |
| 3-630 | Me | 1 | H | 4-[MeO-$(CH_2)_3$]-Ph |
| 3-631 | Me | 1 | H | 3-[MeO-$(CH_2)_3$]-Ph |
| 3-632 | Me | 1 | H | 4-(EtO-$CH_2$)-Ph |
| 3-633 | Me | 1 | H | 3-(EtO-$CH_2$)-Ph |
| 3-634 | Me | 1 | H | 4-[EtO-$(CH_2)_2$]-Ph |
| 3-635 | Me | 1 | H | 3-[EtO-$(CH_2)_2$]-Ph |
| 3-636 | Me | 1 | H | 4-[EtO-$(CH_2)_3$]-Ph |
| 3-637 | Me | 1 | H | 3-[EtO-$(CH_2)_3$]-Ph |

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| 3-638 | Me | 1 | H | 4-cPrO-Ph |
| 3-639 | Me | 1 | H | 3-cPrO-Ph |
| 3-640 | Me | 1 | H | 4-(cPrO-$CH_2$)-Ph |
| 3-641 | Me | 1 | H | 3-(cPrO-$CH_2$)-Ph |
| 3-642 | Me | 1 | H | 4-[cPrO-$(CH_2)_2$]-Ph |
| 3-643 | Me | 1 | H | 3-[cPrO-$(CH_2)_2$]-Ph |
| 3-644 | Me | 1 | H | 4-[cPrO-$(CH_2)_3$]-Ph |
| 3-645 | Me | 1 | H | 3-[cPrO-$(CH_2)_3$]-Ph |
| 3-646 | Me | 1 | H | 4-$CHF_2O$-Ph |
| 3-647 | Me | 1 | H | 3-$CHF_2O$-Ph |
| 3-648 | Me | 1 | H | 4-($CHF_2O$-$CH_2$)-Ph |
| 3-649 | Me | 1 | H | 3-($CHF_2O$-$CH_2$)-Ph |
| 3-650 | Me | 1 | H | 4-[$CHF_2O$-$(CH_2)_2$]-Ph |
| 3-651 | Me | 1 | H | 3-[$CHF_2O$-$(CH_2)_2$]-Ph |
| 3-652 | Me | 1 | H | 4-[$CHF_2O$-$(CH_2)_3$]-Ph |
| 3-653 | Me | 1 | H | 3-[$CHF_2O$-$(CH_2)_3$]-Ph |
| 3-654 | Me | 1 | H | 3-($H_2NCO$)-Ph |
| 3-655 | Me | 1 | H | 4-($H_2NCO$-$CH_2$)-Ph |
| 3-656 | Me | 1 | H | 3-($H_2NCO$-$CH_2$)-Ph |
| 3-657 | Me | 1 | H | 4-[$H_2NCO$-$(CH_2)_2$]-Ph |
| 3-658 | Me | 1 | H | 3-[$H_2NCO$-$(CH_2)_2$]-Ph |
| 3-659 | Me | 1 | H | 3-(MeNHCO)-Ph |
| 3-660 | Me | 1 | H | 4-(MeNHCO-$CH_2$)-Ph |
| 3-661 | Me | 1 | H | 3-(MeNHCO-$CH_2$)-Ph |
| 3-662 | Me | 1 | H | 4-[MeNHCO-$(CH_2)_2$]-Ph |
| 3-663 | Me | 1 | H | 3-[MeNHCO-$(CH_2)_2$]-Ph |
| 3-664 | Me | 1 | H | 4-(iPrNHCO)-Ph |

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|---|---|---|---|---|
| 3-665 | Me | 1 | H | 3-(iPrNHCO)-Ph |
| 3-666 | Me | 1 | H | 4-(iPrNHCO-$CH_2$)-Ph |
| 3-667 | Me | 1 | H | 3-(iPrNHCO-$CH_2$)-Ph |
| 3-668 | Me | 1 | H | 4-[iPrNHCO-$(CH_2)_2$]-Ph |
| 3-669 | Me | 1 | H | 3-[iPrNHCO-$(CH_2)_2$]-Ph |
| 3-670 | Me | 1 | H | 4-(EtNMeCO)-Ph |
| 3-671 | Me | 1 | H | 3-(EtNMeCO)-Ph |
| 3-672 | Me | 1 | H | 4-(EtNMeCO-$CH_2$)-Ph |
| 3-673 | Me | 1 | H | 3-(EtNMeCO-$CH_2$)-Ph |
| 3-674 | Me | 1 | H | 4-[EtNMeCO-$(CH_2)_2$]-Ph |
| 3-675 | Me | 1 | H | 3-[EtNMeCO-$(CH_2)_2$]-Ph |
| 3-676 | Me | 1 | H | 3-($Me_2$NCO)-Ph |
| 3-677 | Me | 1 | H | 4-($Me_2$NCO-$CH_2$)-Ph |
| 3-678 | Me | 1 | H | 3-($Me_2$NCO-$CH_2$)-Ph |
| 3-679 | Me | 1 | H | 4-[$Me_2$NCO-$(CH_2)_2$]-Ph |
| 3-680 | Me | 1 | H | 3-[$Me_2$NCO-$(CH_2)_2$]-Ph |
| 3-681 | Me | 1 | H | 3-($Et_2$NCO)-Ph |
| 3-682 | Me | 1 | H | 4-($Et_2$NCO-$CH_2$)-Ph |
| 3-683 | Me | 1 | H | 3-($Et_2$NCO-$CH_2$)-Ph |
| 3-684 | Me | 1 | H | 4-[$Et_2$NCO-$(CH_2)_2$]-Ph |
| 3-685 | Me | 1 | H | 3-[$Et_2$NCO-$(CH_2)_2$]-Ph |
| 3-686 | Me | 1 | H | 4-[(MeO)NMeCO]-Ph |
| 3-687 | Me | 1 | H | 3-[(MeO)NMeCO]-Ph |
| 3-688 | Me | 1 | H | 4-[(MeO)NMeCO-$CH_2$]-Ph |
| 3-689 | Me | 1 | H | 3-[(MeO)NMeCO-$CH_2$]-Ph |
| 3-690 | Me | 1 | H | 4-[(MeO)NMeCO-$(CH_2)_2$]-Ph |
| 3-691 | Me | 1 | H | 3-[(MeO)NMeCO-$(CH_2)_2$]-Ph |

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|---|---|---|---|---|
| 3-692 | Me | 1 | H | 4-(Aze-CO)-Ph |
| 3-693 | Me | 1 | H | 3-(Aze-CO)-Ph |
| 3-694 | Me | 1 | H | 4-(Aze-CO-$CH_2$)-Ph |
| 3-695 | Me | 1 | H | 3-(Aze-CO-$CH_2$)-Ph |
| 3-696 | Me | 1 | H | 4-[Aze-CO-$(CH_2)_2$]-Ph |
| 3-697 | Me | 1 | H | 3-[Aze-CO-$(CH_2)_2$]-Ph |
| 3-698 | Me | 1 | H | 4-[(3-HO-1-Aze)-CO]-Ph |
| 3-699 | Me | 1 | H | 3-[(3-HO-1-Aze)-CO]-Ph |
| 3-700 | Me | 1 | H | 4-[(3-HO-Aze)-CO-$CH_2$]-Ph |
| 3-701 | Me | 1 | H | 3-[(3-HO-Aze)-CO-$CH_2$]-Ph |
| 3-702 | Me | 1 | H | 4-[(3-HO-Aze)-CO-$(CH_2)_2$]-Ph |
| 3-703 | Me | 1 | H | 3-[(3-HO-Aze)-CO-$(CH_2)_2$]-Ph |
| 3-704 | Me | 1 | H | 4-(Pyrld-CO)-Ph |
| 3-705 | Me | 1 | H | 3-(Pyrld-CO)-Ph |
| 3-706 | Me | 1 | H | 4-(Pyrld-CO-$CH_2$)-Ph |
| 3-707 | Me | 1 | H | 3-(Pyrld-CO-$CH_2$)-Ph |
| 3-708 | Me | 1 | H | 4-[Pyrld-CO-$(CH_2)_2$]-Ph |
| 3-709 | Me | 1 | H | 3-[Pyrld-CO-$(CH_2)_2$]-Ph |
| 3-710 | Me | 1 | H | 4-(Pipo-CO)-Ph |
| 3-711 | Me | 1 | H | 3-(Pipo-CO)-Ph |
| 3-712 | Me | 1 | H | 4-(Pipo-CO-$CH_2$)-Ph |
| 3-713 | Me | 1 | H | 3-(Pipo-CO-$CH_2$)-Ph |
| 3-714 | Me | 1 | H | 4-[Pipo-CO-$(CH_2)_2$]-Ph |
| 3-715 | Me | 1 | H | 3-[Pipo-CO-$(CH_2)_2$]-Ph |
| 3-716 | Me | 1 | H | 4-[(4-Me-Pipra)-CO]-Ph |
| 3-717 | Me | 1 | H | 3-[(4-Me-Pipra)-CO]-Ph |
| 3-718 | Me | 1 | H | 4-[(4-Me-Pipra)-CO-$CH_2$]-Ph |

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|---|---|---|---|---|
| 3-719 | Me | 1 | H | 3-[(4-Me-Pipra)-CO-$CH_2$]-Ph |
| 3-720 | Me | 1 | H | 4-[(4-Me-Pipra)-CO-$(CH_2)_2$]-Ph |
| 3-721 | Me | 1 | H | 3-[(4-Me-Pipra)-CO-$(CH_2)_2$]-Ph |
| 3-722 | Me | 1 | H | 4-(Mor-CO)-Ph |
| 3-723 | Me | 1 | H | 3-(Mor-CO)-Ph |
| 3-724 | Me | 1 | H | 4-(Mor-CO-$CH_2$)-Ph |
| 3-725 | Me | 1 | H | 3-(Mor-CO-$CH_2$)-Ph |
| 3-726 | Me | 1 | H | 4-[Mor-CO-$(CH_2)_2$]-Ph |
| 3-727 | Me | 1 | H | 3-[Mor-CO-$(CH_2)_2$]-Ph |
| 3-728 | Me | 1 | H | 3-$Me_2N$-Ph |
| 3-729 | Me | 1 | H | 4-($Me_2N$-$CH_2$)-Ph |
| 3-730 | Me | 1 | H | 3-($Me_2N$-$CH_2$)-Ph |
| 3-731 | Me | 1 | H | 4-[$Me_2N$-$(CH_2)_2$]-Ph |
| 3-732 | Me | 1 | H | 3-[$Me_2N$-$(CH_2)_2$]-Ph |
| 3-733 | Me | 1 | H | 4-[$Me_2N$-$(CH_2)_3$]-Ph |
| 3-734 | Me | 1 | H | 3-[$Me_2N$-$(CH_2)_3$]-Ph |
| 3-735 | Me | 1 | H | 4-Mor-Ph |
| 3-736 | Me | 1 | H | 3-Mor-Ph |
| 3-737 | Me | 1 | H | 4-(Mor-$CH_2$)-Ph |
| 3-738 | Me | 1 | H | 3-(Mor-$CH_2$)-Ph |
| 3-739 | Me | 1 | H | 4-[Mor-$(CH_2)_2$]-Ph |
| 3-740 | Me | 1 | H | 3-[Mor-$(CH_2)_2$]-Ph |
| 3-741 | Me | 1 | H | 4-[Mor-$(CH_2)_3$]-Ph |
| 3-742 | Me | 1 | H | 3-[Mor-$(CH_2)_3$]-Ph |
| 3-743 | Me | 1 | H | 4-Pipo-Ph |
| 3-744 | Me | 1 | H | 3-Pipo-Ph |
| 3-745 | Me | 1 | H | 4-(Pipo-$CH_2$)-Ph |

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|---|---|---|---|---|
| 3-746 | Me | 1 | H | 3-(Pipo-$CH_2$)-Ph |
| 3-747 | Me | 1 | H | 4-[Pipo-$(CH_2)_2$]-Ph |
| 3-748 | Me | 1 | H | 3-[Pipo-$(CH_2)_2$]-Ph |
| 3-749 | Me | 1 | H | 4-[Pipo-$(CH_2)_3$]-Ph |
| 3-750 | Me | 1 | H | 3-[Pipo-$(CH_2)_3$]-Ph |
| 3-751 | Me | 1 | H | 4-HO-Ph |
| 3-752 | Me | 1 | H | 3-HO-Ph |
| 3-753 | Me | 1 | H | 4-(HO-$CH_2$)-Ph |
| 3-754 | Me | 1 | H | 3-(HO-$CH_2$)-Ph |
| 3-755 | Me | 1 | H | 4-[HO-$(CH_2)_2$]-Ph |
| 3-756 | Me | 1 | H | 3-[HO-$(CH_2)_2$]-Ph |
| 3-757 | Me | 1 | H | 4-[HO-$(CH_2)_3$]-Ph |
| 3-758 | Me | 1 | H | 3-[HO-$(CH_2)_3$]-Ph |
| 3-759 | Me | 1 | H | 4-[MeCH(OH)]-Ph |
| 3-760 | Me | 1 | H | 3-[MeCH(OH)]-Ph |
| 3-761 | Me | 1 | H | 4-[MeCH(OH)-$CH_2$]-Ph |
| 3-762 | Me | 1 | H | 3-[MeCH(OH)-$CH_2$]-Ph |
| 3-763 | Me | 1 | H | 4-[MeCH(OH)-$(CH_2)_2$]-Ph |
| 3-764 | Me | 1 | H | 3-[MeCH(OH)-$(CH_2)_2$]-Ph |
| 3-765 | Me | 1 | H | 3-CN-Ph |
| 3-766 | Me | 1 | H | 4-(CN-$CH_2$)-Ph |
| 3-767 | Me | 1 | H | 3-(CN-$CH_2$)-Ph |
| 3-768 | Me | 1 | H | 4-[CN-$(CH_2)_2$]-Ph |
| 3-769 | Me | 1 | H | 3-[CN-$(CH_2)_2$]-Ph |
| 3-770 | Me | 1 | H | 3-Ac-Ph |
| 3-771 | Me | 1 | H | 4-(Ac-$CH_2$)-Ph |
| 3-772 | Me | 1 | H | 3-(Ac-$CH_2$)-Ph |

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|---|---|---|---|---|
| 3-773 | Me | 1 | H | 4-[Ac-$(CH_2)_2$]-Ph |
| 3-774 | Me | 1 | H | 3-[Ac-$(CH_2)_2$]-Ph |
| 3-775 | Me | 1 | H | 4-($CF_3CO$)-Ph |
| 3-776 | Me | 1 | H | 4-(EtCO)-Ph |
| 3-777 | Me | 1 | H | 3-(EtCO)-Ph |
| 3-778 | Me | 1 | H | 4-(EtCO-$CH_2$)-Ph |
| 3-779 | Me | 1 | H | 3-(EtCO-$CH_2$)-Ph |
| 3-780 | Me | 1 | H | 4-[EtCO-$(CH_2)_2$]-Ph |
| 3-781 | Me | 1 | H | 3-[EtCO-$(CH_2)_2$]-Ph |
| 3-782 | Me | 1 | H | 4-(iPrCO)-Ph |
| 3-783 | Me | 1 | H | 4-(cBuCO)-Ph |
| 3-784 | Me | 1 | H | 4-(cPrCO)-Ph |
| 3-785 | Me | 1 | H | 4-(Ph-CO)-Ph |
| 3-786 | Me | 1 | H | 4-Ac-3-MeO-Ph |
| 3-787 | Me | 1 | H | 4-Ac-3-OH-Ph |
| 3-788 | Me | 1 | H | 4-Ac-3-Cl-Ph |
| 3-789 | Me | 1 | H | 4-[$CH_3C$(=N-OH)]-Ph |
| 3-790 | Me | 1 | H | 3-[$CH_3C$(=N-OH)]-Ph |
| 3-791 | Me | 1 | H | 4-[$CH_3C$(=N-OH)-$CH_2$]-Ph |
| 3-792 | Me | 1 | H | 3-[$CH_3C$(=N-OH)-$CH_2$]-Ph |
| 3-793 | Me | 1 | H | 4-[$CH_3C$(=N-OH)-$(CH_2)_2$]-Ph |
| 3-794 | Me | 1 | H | 3-[$CH_3C$(=N-OH)-$(CH_2)_2$]-Ph |
| 3-795 | Me | 1 | H | 4-[$CH_3C$(=N-OMe)]-Ph |
| 3-796 | Me | 1 | H | 3-[$CH_3C$(=N-OMe)]-Ph |
| 3-797 | Me | 1 | H | 4-[$CH_3C$(=N-OMe)-$CH_2$]-Ph |
| 3-798 | Me | 1 | H | 3-[$CH_3C$(=N-OMe)-$CH_2$]-Ph |
| 3-799 | Me | 1 | H | 4-[$CH_3C$(=N-OMe)-$(CH_2)_2$]-Ph |

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|---|---|---|---|---|
| 3-800 | Me | 1 | H | 3-[$CH_3C(=N\text{-}OMe)\text{-}(CH_2)_2$]-Ph |
| 3-801 | Me | 1 | H | 4-($Me_2NSO_2$)-Ph |
| 3-802 | Me | 1 | H | 4-[$(MeO)_2CH$]-Ph |
| 3-803 | Me | 1 | H | 3-[$(MeO)_2CH$]-Ph |
| 3-804 | Me | 1 | H | 4-[$(MeO)_2CH\text{-}CH_2$]-Ph |
| 3-805 | Me | 1 | H | 3-[$(MeO)_2CH\text{-}CH_2$]-Ph |
| 3-806 | Me | 1 | H | 4-[$(MeO)_2CH\text{-}(CH_2)_2$]-Ph |
| 3-807 | Me | 1 | H | 3-[$(MeO)_2CH\text{-}(CH_2)_2$]-Ph |
| 3-808 | Me | 1 | H | 4-[$Me(MeO)_2C$]-Ph |
| 3-809 | Me | 1 | H | 3-[$Me(MeO)_2C$]-Ph |
| 3-810 | Me | 1 | H | 4-[$Me(MeO)_2C\text{-}CH_2$]-Ph |
| 3-811 | Me | 1 | H | 3-[$Me(MeO)_2C\text{-}CH_2$]-Ph |
| 3-812 | Me | 1 | H | 4-[$Me(MeO)_2C\text{-}(CH_2)_2$]-Ph |
| 3-813 | Me | 1 | H | 3-[$Me(MeO)_2C\text{-}(CH_2)_2$]-Ph |
| 3-814 | Me | 1 | H | 4-[$(EtO)_2CH$]-Ph |
| 3-815 | Me | 1 | H | 3-[$(EtO)_2CH$]-Ph |
| 3-816 | Me | 1 | H | 4-[$(EtO)_2CH\text{-}CH_2$]-Ph |
| 3-817 | Me | 1 | H | 3-[$(EtO)_2CH\text{-}CH_2$]-Ph |
| 3-818 | Me | 1 | H | 4-[$(EtO)_2CH\text{-}(CH_2)_2$]-Ph |
| 3-819 | Me | 1 | H | 3-[$(EtO)_2CH\text{-}(CH_2)_2$]-Ph |
| 3-820 | Me | 1 | H | 4-[$Me(EtO)_2C$]-Ph |
| 3-821 | Me | 1 | H | 3-[$Me(EtO)_2C$]-Ph |
| 3-822 | Me | 1 | H | 4-[$Me(EtO)_2C\text{-}CH_2$]-Ph |
| 3-823 | Me | 1 | H | 3-[$Me(EtO)_2C\text{-}CH_2$]-Ph |
| 3-824 | Me | 1 | H | 4-[$Me(EtO)_2C\text{-}(CH_2)_2$]-Ph |
| 3-825 | Me | 1 | H | 3-[$Me(EtO)_2C\text{-}(CH_2)_2$]-Ph |
| 3-826 | Me | 1 | H | 4-(2-Dioxo)-Ph |

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|---|---|---|---|---|
| 3-827 | Me | 1 | H | 3-(2-Dioxo)-Ph |
| 3-828 | Me | 1 | H | 4-[(2-Dioxo)-$CH_2$]-Ph |
| 3-829 | Me | 1 | H | 3-[(2-Dioxo)-$CH_2$]-Ph |
| 3-830 | Me | 1 | H | 4-[(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-831 | Me | 1 | H | 3-[(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-832 | Me | 1 | H | 4-[2-Me-(2-Dioxo)]-Ph |
| 3-833 | Me | 1 | H | 3-[2-Me-(2-Dioxo)]-Ph |
| 3-834 | Me | 1 | H | 4-[2-Me-(2-Dioxo)-$CH_2$]-Ph |
| 3-835 | Me | 1 | H | 3-[2-Me-(2-Dioxo)-$CH_2$]-Ph |
| 3-836 | Me | 1 | H | 4-[2-Me-(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-837 | Me | 1 | H | 3-[2-Me-(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-838 | Me | 1 | H | 4-(2-Dioxa)-Ph |
| 3-839 | Me | 1 | H | 3-(2-Dioxa)-Ph |
| 3-840 | Me | 1 | H | 4-[(2-Dioxa)-$CH_2$]-Ph |
| 3-841 | Me | 1 | H | 3-[(2-Dioxa)-$CH_2$]-Ph |
| 3-842 | Me | 1 | H | 4-[(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-843 | Me | 1 | H | 3-[(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-844 | Me | 1 | H | 4-[2-Me-(2-Dioxa)]-Ph |
| 3-845 | Me | 1 | H | 3-[2-Me-(2-Dioxa)]-Ph |
| 3-846 | Me | 1 | H | 4-[2-Me-(2-Dioxa)-$CH_2$]-Ph |
| 3-847 | Me | 1 | H | 3-[2-Me-(2-Dioxa)-$CH_2$]-Ph |
| 3-848 | Me | 1 | H | 4-[2-Me-(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-849 | Me | 1 | H | 3-[2-Me-(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-850 | Me | 1 | H | 2-Me-1-oxo-5-IIndn |
| 3-851 | Me | 1 | H | 6-BzOxaz |
| 3-852 | Me | 1 | H | 4-(HO-N=)-7-Chr |
| 3-853 | Me | 1 | H | 3-Me-6-BzIox |

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|---|---|---|---|---|
| 3-854 | Me | 1 | H | 2-Me-6-BzOxaz |
| 3-855 | Me | 1 | H | 2-Me-5-BzOxaz |
| 3-856 | Me | 1 | H | 2,3-dihydro-5-BzFur |
| 3-857 | Me | 1 | H | 6-Qui |
| 3-858 | Me | 1 | H | 6-Iqui |
| 3-859 | Me | 1 | H | 3-(HO-N=)-2,3-dihydro-6-BzFur |
| 3-860 | Me | 1 | H | 2-Me-6-BzThaz |
| 3-861 | Me | 1 | H | 5-Ind |
| 3-862 | Me | 1 | H | 4-Ac-2-Thaz |
| 3-863 | Me | 1 | H | 5-Ac-2-Thi |
| 3-864 | Me | 1 | H | 5-Ac-2-Fur |
| 3-865 | Me | 1 | H | 5-$Me_2NCO$-2-Py |
| 3-866 | Me | 1 | H | 5-($Me_2NCO$-$CH_2$)-2-Py |
| 3-867 | Me | 1 | H | 5-[$Me_2NCO$-$(CH_2)_2$]-2-Py |
| 3-868 | Me | 1 | H | 4-$Me_2NCO$-2-Thaz |
| 3-869 | Me | 1 | H | 5-$Me_2NCO$-2-Thaz |
| 3-870 | Me | 1 | H | 4-($Me_2NCO$-$CH_2$)-2-Thaz |
| 3-871 | Me | 1 | H | 5-($Me_2NCO$-$CH_2$)-2-Thaz |
| 3-872 | Me | 1 | H | 2-Thazn |
| 3-873 | Me | 1 | H | 2-Oxazn |
| 3-874 | H | 2 | H | 4-(MeO-$CH_2$)-Ph |
| 3-875 | H | 2 | H | 3-(MeO-$CH_2$)-Ph |
| 3-876 | H | 2 | H | 4-[MeO-$(CH_2)_2$]-Ph |
| 3-877 | H | 2 | H | 3-[MeO-$(CH_2)_2$]-Ph |
| 3-878 | H | 2 | H | 4-[MeO-$(CH_2)_3$]-Ph |
| 3-879 | H | 2 | H | 3-[MeO-$(CH_2)_3$]-Ph |
| 3-880 | H | 2 | H | 4-(EtO-$CH_2$)-Ph |

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| 3-881 | H | 2 | H | 3-(EtO-$CH_2$)-Ph |
| 3-882 | H | 2 | H | 4-[EtO-$(CH_2)_2$]-Ph |
| 3-883 | H | 2 | H | 3-[EtO-$(CH_2)_2$]-Ph |
| 3-884 | H | 2 | H | 4-[EtO-$(CH_2)_3$]-Ph |
| 3-885 | H | 2 | H | 3-[EtO-$(CH_2)_3$]-Ph |
| 3-886 | H | 2 | H | 4-cPrO-Ph |
| 3-887 | H | 2 | H | 3-cPrO-Ph |
| 3-888 | H | 2 | H | 4-(cPrO-$CH_2$)-Ph |
| 3-889 | H | 2 | H | 3-(cPrO-$CH_2$)-Ph |
| 3-890 | H | 2 | H | 4-[cPrO-$(CH_2)_2$]-Ph |
| 3-891 | H | 2 | H | 3-[cPrO-$(CH_2)_2$]-Ph |
| 3-892 | H | 2 | H | 4-[cPrO-$(CH_2)_3$]-Ph |
| 3-893 | H | 2 | H | 3-[cPrO-$(CH_2)_3$]-Ph |
| 3-894 | H | 2 | H | 4-$CHF_2O$-Ph |
| 3-895 | H | 2 | H | 3-$CHF_2O$-Ph |
| 3-896 | H | 2 | H | 4-($CHF_2O$-$CH_2$)-Ph |
| 3-897 | H | 2 | H | 3-($CHF_2O$-$CH_2$)-Ph |
| 3-898 | H | 2 | H | 4-[$CHF_2O$-$(CH_2)_2$]-Ph |
| 3-899 | H | 2 | H | 3-[$CHF_2O$-$(CH_2)_2$]-Ph |
| 3-900 | H | 2 | H | 4-[$CHF_2O$-$(CH_2)_3$]-Ph |
| 3-901 | H | 2 | H | 3-[$CHF_2O$-$(CH_2)_3$]-Ph |
| 3-902 | H | 2 | H | 3-($H_2NCO$)-Ph |
| 3-903 | H | 2 | H | 4-($H_2NCO$-$CH_2$)-Ph |
| 3-904 | H | 2 | H | 3-($H_2NCO$-$CH_2$)-Ph |
| 3-905 | H | 2 | H | 4-[$H_2NCO$-$(CH_2)_2$]-Ph |
| 3-906 | H | 2 | H | 3-[$H_2NCO$-$(CH_2)_2$]-Ph |
| 3-907 | H | 2 | H | 3-(MeNHCO)-Ph |

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| 3-908 | H | 2 | H | 4-(MeNHCO-$CH_2$)-Ph |
| 3-909 | H | 2 | H | 3-(MeNHCO-$CH_2$)-Ph |
| 3-910 | H | 2 | H | 4-[MeNHCO-$(CH_2)_2$]-Ph |
| 3-911 | H | 2 | H | 3-[MeNHCO-$(CH_2)_2$]-Ph |
| 3-912 | H | 2 | H | 4-(iPrNHCO)-Ph |
| 3-913 | H | 2 | H | 3-(iPrNHCO)-Ph |
| 3-914 | H | 2 | H | 4-(iPrNHCO-$CH_2$)-Ph |
| 3-915 | H | 2 | H | 3-(iPrNHCO-$CH_2$)-Ph |
| 3-916 | H | 2 | H | 4-[iPrNHCO-$(CH_2)_2$]-Ph |
| 3-917 | H | 2 | H | 3-[iPrNHCO-$(CH_2)_2$]-Ph |
| 3-918 | H | 2 | H | 4-(EtNMeCO)-Ph |
| 3-919 | H | 2 | H | 3-(EtNMeCO)-Ph |
| 3-920 | H | 2 | H | 4-(EtNMeCO-$CH_2$)-Ph |
| 3-921 | H | 2 | H | 3-(EtNMeCO-$CH_2$)-Ph |
| 3-922 | H | 2 | H | 4-[EtNMeCO-$(CH_2)_2$]-Ph |
| 3-923 | H | 2 | H | 3-[EtNMeCO-$(CH_2)_2$]-Ph |
| 3-924 | H | 2 | H | 3-($Me_2$NCO)-Ph |
| 3-925 | H | 2 | H | 4-($Me_2$NCO-$CH_2$)-Ph |
| 3-926 | H | 2 | H | 3-($Me_2$NCO-$CH_2$)-Ph |
| 3-927 | H | 2 | H | 4-[$Me_2$NCO-$(CH_2)_2$]-Ph |
| 3-928 | H | 2 | H | 3-[$Me_2$NCO-$(CH_2)_2$]-Ph |
| 3-929 | H | 2 | H | 3-($Et_2$NCO)-Ph |
| 3-930 | H | 2 | H | 4-($Et_2$NCO-$CH_2$)-Ph |
| 3-931 | H | 2 | H | 3-($Et_2$NCO-$CH_2$)-Ph |
| 3-932 | H | 2 | H | 4-[$Et_2$NCO-$(CH_2)_2$]-Ph |
| 3-933 | H | 2 | H | 3-[$Et_2$NCO-$(CH_2)_2$]-Ph |
| 3-934 | H | 2 | H | 4-[(MeO)NMeCO]-Ph |

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|---|---|---|---|---|
| 3-935 | H | 2 | H | 3-[(MeO)NMeCO]-Ph |
| 3-936 | H | 2 | H | 4-[(MeO)NMeCO-$CH_2$]-Ph |
| 3-937 | H | 2 | H | 3-[(MeO)NMeCO-$CH_2$]-Ph |
| 3-938 | H | 2 | H | 4-[(MeO)NMeCO-$(CH_2)_2$]-Ph |
| 3-939 | H | 2 | H | 3-[(MeO)NMeCO-$(CH_2)_2$]-Ph |
| 3-940 | H | 2 | H | 4-(Aze-CO)-Ph |
| 3-941 | H | 2 | H | 3-(Aze-CO)-Ph |
| 3-942 | H | 2 | H | 4-(Aze-CO-$CH_2$)-Ph |
| 3-943 | H | 2 | H | 3-(Aze-CO-$CH_2$)-Ph |
| 3-944 | H | 2 | H | 4-[Aze-CO-$(CH_2)_2$]-Ph |
| 3-945 | H | 2 | H | 3-[Aze-CO-$(CH_2)_2$]-Ph |
| 3-946 | H | 2 | H | 4-[(3-HO-1-Aze)-CO]-Ph |
| 3-947 | H | 2 | H | 3-[(3-HO-1-Aze)-CO]-Ph |
| 3-948 | H | 2 | H | 4-[(3-HO-Aze)-CO-$CH_2$]-Ph |
| 3-949 | H | 2 | H | 3-[(3-HO-Aze)-CO-$CH_2$]-Ph |
| 3-950 | H | 2 | H | 4-[(3-HO-Aze)-CO-$(CH_2)_2$]-Ph |
| 3-951 | H | 2 | H | 3-[(3-HO-Aze)-CO-$(CH_2)_2$]-Ph |
| 3-952 | H | 2 | H | 4-(Pyrld-CO)-Ph |
| 3-953 | H | 2 | H | 3-(Pyrld-CO)-Ph |
| 3-954 | H | 2 | H | 4-(Pyrld-CO-$CH_2$)-Ph |
| 3-955 | H | 2 | H | 3-(Pyrld-CO-$CH_2$)-Ph |
| 3-956 | H | 2 | H | 4-[Pyrld-CO-$(CH_2)_2$]-Ph |
| 3-957 | H | 2 | H | 3-[Pyrld-CO-$(CH_2)_2$]-Ph |
| 3-958 | H | 2 | H | 4-(Pipo-CO)-Ph |
| 3-959 | H | 2 | H | 3-(Pipo-CO)-Ph |
| 3-960 | H | 2 | H | 4-(Pipo-CO-$CH_2$)-Ph |
| 3-961 | H | 2 | H | 3-(Pipo-CO-$CH_2$)-Ph |

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|---|---|---|---|---|
| 3-962 | H | 2 | H | 4-[Pipo-CO-$(CH_2)_2$]-Ph |
| 3-963 | H | 2 | H | 3-[Pipo-CO-$(CH_2)_2$]-Ph |
| 3-964 | H | 2 | H | 4-[(4-Me-Pipra)-CO]-Ph |
| 3-965 | H | 2 | H | 3-[(4-Me-Pipra)-CO]-Ph |
| 3-966 | H | 2 | H | 4-[(4-Me-Pipra)-CO-$CH_2$]-Ph |
| 3-967 | H | 2 | H | 3-[(4-Me-Pipra)-CO-$CH_2$]-Ph |
| 3-968 | H | 2 | H | 4-[(4-Me-Pipra)-CO-$(CH_2)_2$]-Ph |
| 3-969 | H | 2 | H | 3-[(4-Me-Pipra)-CO-$(CH_2)_2$]-Ph |
| 3-970 | H | 2 | H | 4-(Mor-CO)-Ph |
| 3-971 | H | 2 | H | 3-(Mor-CO)-Ph |
| 3-972 | H | 2 | H | 4-(Mor-CO-$CH_2$)-Ph |
| 3-973 | H | 2 | H | 3-(Mor-CO-$CH_2$)-Ph |
| 3-974 | H | 2 | H | 4-[Mor-CO-$(CH_2)_2$]-Ph |
| 3-975 | H | 2 | H | 3-[Mor-CO-$(CH_2)_2$]-Ph |
| 3-976 | H | 2 | H | 3-$Me_2N$-Ph |
| 3-977 | H | 2 | H | 4-($Me_2N$-$CH_2$)-Ph |
| 3-978 | H | 2 | H | 3-($Me_2N$-$CH_2$)-Ph |
| 3-979 | H | 2 | H | 4-[$Me_2N$-$(CH_2)_2$]-Ph |
| 3-980 | H | 2 | H | 3-[$Me_2N$-$(CH_2)_2$]-Ph |
| 3-981 | H | 2 | H | 4-[$Me_2N$-$(CH_2)_3$]-Ph |
| 3-982 | H | 2 | H | 3-[$Me_2N$-$(CH_2)_3$]-Ph |
| 3-983 | H | 2 | H | 4-Mor-Ph |
| 3-984 | H | 2 | H | 3-Mor-Ph |
| 3-985 | H | 2 | H | 4-(Mor-$CH_2$)-Ph |
| 3-986 | H | 2 | H | 3-(Mor-$CH_2$)-Ph |
| 3-987 | H | 2 | H | 4-[Mor-$(CH_2)_2$]-Ph |
| 3-988 | H | 2 | H | 3-[Mor-$(CH_2)_2$]-Ph |

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|---|---|---|---|---|
| 3-989 | H | 2 | H | 4-[Mor-$(CH_2)_3$]-Ph |
| 3-990 | H | 2 | H | 3-[Mor-$(CH_2)_3$]-Ph |
| 3-991 | H | 2 | H | 4-Pipo-Ph |
| 3-992 | H | 2 | H | 3-Pipo-Ph |
| 3-993 | H | 2 | H | 4-(Pipo-$CH_2$)-Ph |
| 3-994 | H | 2 | H | 3-(Pipo-$CH_2$)-Ph |
| 3-995 | H | 2 | H | 4-[Pipo-$(CH_2)_2$]-Ph |
| 3-996 | H | 2 | H | 3-[Pipo-$(CH_2)_2$]-Ph |
| 3-997 | H | 2 | H | 4-[Pipo-$(CH_2)_3$]-Ph |
| 3-998 | H | 2 | H | 3-[Pipo-$(CH_2)_3$]-Ph |
| 3-999 | H | 2 | H | 4-HO-Ph |
| 3-1000 | H | 2 | H | 3-HO-Ph |
| 3-1001 | H | 2 | H | 4-(HO-$CH_2$)-Ph |
| 3-1002 | H | 2 | H | 3-(HO-$CH_2$)-Ph |
| 3-1003 | H | 2 | H | 4-[HO-$(CH_2)_2$]-Ph |
| 3-1004 | H | 2 | H | 3-[HO-$(CH_2)_2$]-Ph |
| 3-1005 | H | 2 | H | 4-[HO-$(CH_2)_3$]-Ph |
| 3-1006 | H | 2 | H | 3-[HO-$(CH_2)_3$]-Ph |
| 3-1007 | H | 2 | H | 4-[MeCH(OH)]-Ph |
| 3-1008 | H | 2 | H | 3-[MeCH(OH)]-Ph |
| 3-1009 | H | 2 | H | 4-[MeCH(OH)-$CH_2$]-Ph |
| 3-1010 | H | 2 | H | 3-[MeCH(OH)-$CH_2$]-Ph |
| 3-1011 | H | 2 | H | 4-[MeCH(OH)-$(CH_2)_2$]-Ph |
| 3-1012 | H | 2 | H | 3-[MeCH(OH)-$(CH_2)_2$]-Ph |
| 3-1013 | H | 2 | H | 3-CN-Ph |
| 3-1014 | H | 2 | H | 4-(CN-$CH_2$)-Ph |
| 3-1015 | H | 2 | H | 3-(CN-$CH_2$)-Ph |

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|---|---|---|---|---|
| 3-1016 | H | 2 | H | 4-[CN-$(CH_2)_2$]-Ph |
| 3-1017 | H | 2 | H | 3-[CN-$(CH_2)_2$]-Ph |
| 3-1018 | H | 2 | H | 3-Ac-Ph |
| 3-1019 | H | 2 | H | 4-(Ac-$CH_2$)-Ph |
| 3-1020 | H | 2 | H | 3-(Ac-$CH_2$)-Ph |
| 3-1021 | H | 2 | H | 4-[Ac-$(CH_2)_2$]-Ph |
| 3-1022 | H | 2 | H | 3-[Ac-$(CH_2)_2$]-Ph |
| 3-1023 | H | 2 | H | 4-($CF_3CO$)-Ph |
| 3-1024 | H | 2 | H | 4-(EtCO)-Ph |
| 3-1025 | H | 2 | H | 3-(EtCO)-Ph |
| 3-1026 | H | 2 | H | 4-(EtCO-$CH_2$)-Ph |
| 3-1027 | H | 2 | H | 3-(EtCO-$CH_2$)-Ph |
| 3-1028 | H | 2 | H | 4-[EtCO-$(CH_2)_2$]-Ph |
| 3-1029 | H | 2 | H | 3-[EtCO-$(CH_2)_2$]-Ph |
| 3-1030 | H | 2 | H | 4-(iPrCO)-Ph |
| 3-1031 | H | 2 | H | 4-(cBuCO)-Ph |
| 3-1032 | H | 2 | H | 4-(cPrCO)-Ph |
| 3-1033 | H | 2 | H | 4-(Ph-CO)-Ph |
| 3-1034 | H | 2 | H | 4-Ac-3-MeO-Ph |
| 3-1035 | H | 2 | H | 4-Ac-3-OH-Ph |
| 3-1036 | H | 2 | H | 4-Ac-3-Cl-Ph |
| 3-1037 | H | 2 | H | 4-[$CH_3C$(=N-OH)]-Ph |
| 3-1038 | H | 2 | H | 3-[$CH_3C$(=N-OH)]-Ph |
| 3-1039 | H | 2 | H | 4-[$CH_3C$(=N-OH)-$CH_2$]-Ph |
| 3-1040 | H | 2 | H | 3-[$CH_3C$(=N-OH)-$CH_2$]-Ph |
| 3-1041 | H | 2 | H | 4-[$CH_3C$(=N-OH)-$(CH_2)_2$]-Ph |
| 3-1042 | H | 2 | H | 3-[$CH_3C$(=N-OH)-$(CH_2)_2$]-Ph |

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|---|---|---|---|---|
| 3-1043 | H | 2 | H | 4-[$CH_3C$(=N-OMe)]-Ph |
| 3-1044 | H | 2 | H | 3-[$CH_3C$(=N-OMe)]-Ph |
| 3-1045 | H | 2 | H | 4-[$CH_3C$(=N-OMe)-$CH_2$]-Ph |
| 3-1046 | H | 2 | H | 3-[$CH_3C$(=N-OMe)-$CH_2$]-Ph |
| 3-1047 | H | 2 | H | 4-[$CH_3C$(=N-OMe)-$(CH_2)_2$]-Ph |
| 3-1048 | H | 2 | H | 3-[$CH_3C$(=N-OMe)-$(CH_2)_2$]-Ph |
| 3-1049 | H | 2 | H | 4-($Me_2NSO_2$)-Ph |
| 3-1050 | H | 2 | H | 4-[$(MeO)_2CH$]-Ph |
| 3-1051 | H | 2 | H | 3-[$(MeO)_2CH$]-Ph |
| 3-1052 | H | 2 | H | 4-[$(MeO)_2CH$-$CH_2$]-Ph |
| 3-1053 | H | 2 | H | 3-[$(MeO)_2CH$-$CH_2$]-Ph |
| 3-1054 | H | 2 | H | 4-[$(MeO)_2CH$-$(CH_2)_2$]-Ph |
| 3-1055 | H | 2 | H | 3-[$(MeO)_2CH$-$(CH_2)_2$]-Ph |
| 3-1056 | H | 2 | H | 4-[$Me(MeO)_2C$]-Ph |
| 3-1057 | H | 2 | H | 3-[$Me(MeO)_2C$]-Ph |
| 3-1058 | H | 2 | H | 4-[$Me(MeO)_2C$-$CH_2$]-Ph |
| 3-1059 | H | 2 | H | 3-[$Me(MeO)_2C$-$CH_2$]-Ph |
| 3-1060 | H | 2 | H | 4-[$Me(MeO)_2C$-$(CH_2)_2$]-Ph |
| 3-1061 | H | 2 | H | 3-[$Me(MeO)_2C$-$(CH_2)_2$]-Ph |
| 3-1062 | H | 2 | H | 4-[$(EtO)_2CH$]-Ph |
| 3-1063 | H | 2 | H | 3-[$(EtO)_2CH$]-Ph |
| 3-1064 | H | 2 | H | 4-[$(EtO)_2CH$-$CH_2$]-Ph |
| 3-1065 | H | 2 | H | 3-[$(EtO)_2CH$-$CH_2$]-Ph |
| 3-1066 | H | 2 | H | 4-[$(EtO)_2CH$-$(CH_2)_2$]-Ph |
| 3-1067 | H | 2 | H | 3-[$(EtO)_2CH$-$(CH_2)_2$]-Ph |
| 3-1068 | H | 2 | H | 4-[$Me(EtO)_2C$]-Ph |
| 3-1069 | H | 2 | H | 3-[$Me(EtO)_2C$]-Ph |

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|---|---|---|---|---|
| 3-1070 | H | 2 | H | 4-[$Me(EtO)_2C$-$CH_2$]-Ph |
| 3-1071 | H | 2 | H | 3-[$Me(EtO)_2C$-$CH_2$]-Ph |
| 3-1072 | H | 2 | H | 4-[$Me(EtO)_2C$-$(CH_2)_2$]-Ph |
| 3-1073 | H | 2 | H | 3-[$Me(EtO)_2C$-$(CH_2)_2$]-Ph |
| 3-1074 | H | 2 | H | 4-(2-Dioxo)-Ph |
| 3-1075 | H | 2 | H | 3-(2-Dioxo)-Ph |
| 3-1076 | H | 2 | H | 4-[(2-Dioxo)-$CH_2$]-Ph |
| 3-1077 | H | 2 | H | 3-[(2-Dioxo)-$CH_2$]-Ph |
| 3-1078 | H | 2 | H | 4-[(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-1079 | H | 2 | H | 3-[(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-1080 | H | 2 | H | 4-[2-Me-(2-Dioxo)]-Ph |
| 3-1081 | H | 2 | H | 3-[2-Me-(2-Dioxo)]-Ph |
| 3-1082 | H | 2 | H | 4-[2-Me-(2-Dioxo)-$CH_2$]-Ph |
| 3-1083 | H | 2 | H | 3-[2-Me-(2-Dioxo)-$CH_2$]-Ph |
| 3-1084 | H | 2 | H | 4-[2-Me-(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-1085 | H | 2 | H | 3-[2-Me-(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-1086 | H | 2 | H | 4-(2-Dioxa)-Ph |
| 3-1087 | H | 2 | H | 3-(2-Dioxa)-Ph |
| 3-1088 | H | 2 | H | 4-[(2-Dioxa)-$CH_2$]-Ph |
| 3-1089 | H | 2 | H | 3-[(2-Dioxa)-$CH_2$]-Ph |
| 3-1090 | H | 2 | H | 4-[(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-1091 | H | 2 | H | 3-[(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-1092 | H | 2 | H | 4-[2-Me-(2-Dioxa)]-Ph |
| 3-1093 | H | 2 | H | 3-[2-Me-(2-Dioxa)]-Ph |
| 3-1094 | H | 2 | H | 4-[2-Me-(2-Dioxa)-$CH_2$]-Ph |
| 3-1095 | H | 2 | H | 3-[2-Me-(2-Dioxa)-$CH_2$]-Ph |
| 3-1096 | H | 2 | H | 4-[2-Me-(2-Dioxa)-$(CH_2)_2$]-Ph |

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|---|---|---|---|---|
| 3-1097 | H | 2 | H | 3-[2-Me-(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-1098 | H | 2 | H | 2-Me-1-oxo-5-IIndn |
| 3-1099 | H | 2 | H | 6-BzOxaz |
| 3-1100 | H | 2 | H | 4-(HO-N=)-7-Chr |
| 3-1101 | H | 2 | H | 3-Me-6-BzIox |
| 3-1102 | H | 2 | H | 2-Me-6-BzOxaz |
| 3-1103 | H | 2 | H | 2-Me-5-BzOxaz |
| 3-1104 | H | 2 | H | 2,3-dihydro-5-BzFur |
| 3-1105 | H | 2 | H | 6-Qui |
| 3-1106 | H | 2 | H | 6-Iqui |
| 3-1107 | H | 2 | H | 3-(HO-N=)-2,3-dihydro-6-BzFur |
| 3-1108 | H | 2 | H | 2-Me-6-BzThaz |
| 3-1109 | H | 2 | H | 5-Ind |
| 3-1110 | H | 2 | H | 4-Ac-2-Thaz |
| 3-1111 | H | 2 | H | 5-Ac-2-Thi |
| 3-1112 | H | 2 | H | 5-Ac-2-Fur |
| 3-1113 | H | 2 | H | 5-$Me_2$NCO-2-Py |
| 3-1114 | H | 2 | H | 5-($Me_2$NCO-$CH_2$)-2-Py |
| 3-1115 | H | 2 | H | 5-[$Me_2$NCO-$(CH_2)_2$]-2-Py |
| 3-1116 | H | 2 | H | 4-$Me_2$NCO-2-Thaz |
| 3-1117 | H | 2 | H | 5-$Me_2$NCO-2-Thaz |
| 3-1118 | H | 2 | H | 4-($Me_2$NCO-$CH_2$)-2-Thaz |
| 3-1119 | H | 2 | H | 5-($Me_2$NCO-$CH_2$)-2-Thaz |
| 3-1120 | H | 2 | H | 2-Thazn |
| 3-1121 | H | 2 | H | 2-Oxazn |
| 3-1122 | Me | 2 | H | 4-(MeO-$CH_2$)-Ph |
| 3-1123 | Me | 2 | H | 3-(MeO-$CH_2$)-Ph |

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|---|---|---|---|---|
| 3-1124 | Me | 2 | H | 4-[MeO-$(CH_2)_2$]-Ph |
| 3-1125 | Me | 2 | H | 3-[MeO-$(CH_2)_2$]-Ph |
| 3-1126 | Me | 2 | H | 4-[MeO-$(CH_2)_3$]-Ph |
| 3-1127 | Me | 2 | H | 3-[MeO-$(CH_2)_3$]-Ph |
| 3-1128 | Me | 2 | H | 4-(EtO-$CH_2$)-Ph |
| 3-1129 | Me | 2 | H | 3-(EtO-$CH_2$)-Ph |
| 3-1130 | Me | 2 | H | 4-[EtO-$(CH_2)_2$]-Ph |
| 3-1131 | Me | 2 | H | 3-[EtO-$(CH_2)_2$]-Ph |
| 3-1132 | Me | 2 | H | 4-[EtO-$(CH_2)_3$]-Ph |
| 3-1133 | Me | 2 | H | 3-[EtO-$(CH_2)_3$]-Ph |
| 3-1134 | Me | 2 | H | 4-cPrO-Ph |
| 3-1135 | Me | 2 | H | 3-cPrO-Ph |
| 3-1136 | Me | 2 | H | 4-(cPrO-$CH_2$)-Ph |
| 3-1137 | Me | 2 | H | 3-(cPrO-$CH_2$)-Ph |
| 3-1138 | Me | 2 | H | 4-[cPrO-$(CH_2)_2$]-Ph |
| 3-1139 | Me | 2 | H | 3-[cPrO-$(CH_2)_2$]-Ph |
| 3-1140 | Me | 2 | H | 4-[cPrO-$(CH_2)_3$]-Ph |
| 3-1141 | Me | 2 | H | 3-[cPrO-$(CH_2)_3$]-Ph |
| 3-1142 | Me | 2 | H | 4-$CHF_2O$-Ph |
| 3-1143 | Me | 2 | H | 3-$CHF_2O$-Ph |
| 3-1144 | Me | 2 | H | 4-($CHF_2O$-$CH_2$)-Ph |
| 3-1145 | Me | 2 | H | 3-($CHF_2O$-$CH_2$)-Ph |
| 3-1146 | Me | 2 | H | 4-[$CHF_2O$-$(CH_2)_2$]-Ph |
| 3-1147 | Me | 2 | H | 3-[$CHF_2O$-$(CH_2)_2$]-Ph |
| 3-1148 | Me | 2 | H | 4-[$CHF_2O$-$(CH_2)_3$]-Ph |
| 3-1149 | Me | 2 | H | 3-[$CHF_2O$-$(CH_2)_3$]-Ph |
| 3-1150 | Me | 2 | H | 3-($H_2NCO$)-Ph |

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|---|---|---|---|---|
| 3-1151 | Me | 2 | H | 4-($H_2NCO$-$CH_2$)-Ph |
| 3-1152 | Me | 2 | H | 3-($H_2NCO$-$CH_2$)-Ph |
| 3-1153 | Me | 2 | H | 4-[$H_2NCO$-$(CH_2)_2$]-Ph |
| 3-1154 | Me | 2 | H | 3-[$H_2NCO$-$(CH_2)_2$]-Ph |
| 3-1155 | Me | 2 | H | 3-(MeNHCO)-Ph |
| 3-1156 | Me | 2 | H | 4-(MeNHCO-$CH_2$)-Ph |
| 3-1157 | Me | 2 | H | 3-(MeNHCO-$CH_2$)-Ph |
| 3-1158 | Me | 2 | H | 4-[MeNHCO-$(CH_2)_2$]-Ph |
| 3-1159 | Me | 2 | H | 3-[MeNHCO-$(CH_2)_2$]-Ph |
| 3-1160 | Me | 2 | H | 4-(iPrNHCO)-Ph |
| 3-1161 | Me | 2 | H | 3-(iPrNHCO)-Ph |
| 3-1162 | Me | 2 | H | 4-(iPrNHCO-$CH_2$)-Ph |
| 3-1163 | Me | 2 | H | 3-(iPrNHCO-$CH_2$)-Ph |
| 3-1164 | Me | 2 | H | 4-[iPrNHCO-$(CH_2)_2$]-Ph |
| 3-1165 | Me | 2 | H | 3-[iPrNHCO-$(CH_2)_2$]-Ph |
| 3-1166 | Me | 2 | H | 4-(EtNMeCO)-Ph |
| 3-1167 | Me | 2 | H | 3-(EtNMeCO)-Ph |
| 3-1168 | Me | 2 | H | 4-(EtNMeCO-$CH_2$)-Ph |
| 3-1169 | Me | 2 | H | 3-(EtNMeCO-$CH_2$)-Ph |
| 3-1170 | Me | 2 | H | 4-[EtNMeCO-$(CH_2)_2$]-Ph |
| 3-1171 | Me | 2 | H | 3-[EtNMeCO-$(CH_2)_2$]-Ph |
| 3-1172 | Me | 2 | H | 3-($Me_2NCO$)-Ph |
| 3-1173 | Me | 2 | H | 4-($Me_2NCO$-$CH_2$)-Ph |
| 3-1174 | Me | 2 | H | 3-($Me_2NCO$-$CH_2$)-Ph |
| 3-1175 | Me | 2 | H | 4-[$Me_2NCO$-$(CH_2)_2$]-Ph |
| 3-1176 | Me | 2 | H | 3-[$Me_2NCO$-$(CH_2)_2$]-Ph |
| 3-1177 | Me | 2 | H | 3-($Et_2NCO$)-Ph |

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| 3-1178 | Me | 2 | H | 4-($Et_2NCO-CH_2$)-Ph |
| 3-1179 | Me | 2 | H | 3-($Et_2NCO-CH_2$)-Ph |
| 3-1180 | Me | 2 | H | 4-[$Et_2NCO-(CH_2)_2$]-Ph |
| 3-1181 | Me | 2 | H | 3-[$Et_2NCO-(CH_2)_2$]-Ph |
| 3-1182 | Me | 2 | H | 4-[(MeO)NMeCO]-Ph |
| 3-1183 | Me | 2 | H | 3-[(MeO)NMeCO]-Ph |
| 3-1184 | Me | 2 | H | 4-[(MeO)NMeCO-$CH_2$]-Ph |
| 3-1185 | Me | 2 | H | 3-[(MeO)NMeCO-$CH_2$]-Ph |
| 3-1186 | Me | 2 | H | 4-[(MeO)NMeCO-$(CH_2)_2$]-Ph |
| 3-1187 | Me | 2 | H | 3-[(MeO)NMeCO-$(CH_2)_2$]-Ph |
| 3-1188 | Me | 2 | H | 4-(Aze-CO)-Ph |
| 3-1189 | Me | 2 | H | 3-(Aze-CO)-Ph |
| 3-1190 | Me | 2 | H | 4-(Aze-CO-$CH_2$)-Ph |
| 3-1191 | Me | 2 | H | 3-(Aze-CO-$CH_2$)-Ph |
| 3-1192 | Me | 2 | H | 4-[Aze-CO-$(CH_2)_2$]-Ph |
| 3-1193 | Me | 2 | H | 3-[Aze-CO-$(CH_2)_2$]-Ph |
| 3-1194 | Me | 2 | H | 4-[(3-HO-1-Aze)-CO]-Ph |
| 3-1195 | Me | 2 | H | 3-[(3-HO-1-Aze)-CO]-Ph |
| 3-1196 | Me | 2 | H | 4-[(3-HO-Aze)-CO-$CH_2$]-Ph |
| 3-1197 | Me | 2 | H | 3-[(3-HO-Aze)-CO-$CH_2$]-Ph |
| 3-1198 | Me | 2 | H | 4-[(3-HO-Aze)-CO-$(CH_2)_2$]-Ph |
| 3-1199 | Me | 2 | H | 3-[(3-HO-Aze)-CO-$(CH_2)_2$]-Ph |
| 3-1200 | Me | 2 | H | 4-(Pyrld-CO)-Ph |
| 3-1201 | Me | 2 | H | 3-(Pyrld-CO)-Ph |
| 3-1202 | Me | 2 | H | 4-(Pyrld-CO-$CH_2$)-Ph |
| 3-1203 | Me | 2 | H | 3-(Pyrld-CO-$CH_2$)-Ph |
| 3-1204 | Me | 2 | H | 4-[Pyrld-CO-$(CH_2)_2$]-Ph |

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| 3-1205 | Me | 2 | H | 3-[Pyrld-CO-$(CH_2)_2$]-Ph |
| 3-1206 | Me | 2 | H | 4-(Pipo-CO)-Ph |
| 3-1207 | Me | 2 | H | 3-(Pipo-CO)-Ph |
| 3-1208 | Me | 2 | H | 4-(Pipo-CO-$CH_2$)-Ph |
| 3-1209 | Me | 2 | H | 3-(Pipo-CO-$CH_2$)-Ph |
| 3-1210 | Me | 2 | H | 4-[Pipo-CO-$(CH_2)_2$]-Ph |
| 3-1211 | Me | 2 | H | 3-[Pipo-CO-$(CH_2)_2$]-Ph |
| 3-1212 | Me | 2 | H | 4-[(4-Me-Pipra)-CO]-Ph |
| 3-1213 | Me | 2 | H | 3-[(4-Me-Pipra)-CO]-Ph |
| 3-1214 | Me | 2 | H | 4-[(4-Me-Pipra)-CO-$CH_2$]-Ph |
| 3-1215 | Me | 2 | H | 3-[(4-Me-Pipra)-CO-$CH_2$]-Ph |
| 3-1216 | Me | 2 | H | 4-[(4-Me-Pipra)-CO-$(CH_2)_2$]-Ph |
| 3-1217 | Me | 2 | H | 3-[(4-Me-Pipra)-CO-$(CH_2)_2$]-Ph |
| 3-1218 | Me | 2 | H | 4-(Mor-CO)-Ph |
| 3-1219 | Me | 2 | H | 3-(Mor-CO)-Ph |
| 3-1220 | Me | 2 | H | 4-(Mor-CO-$CH_2$)-Ph |
| 3-1221 | Me | 2 | H | 3-(Mor-CO-$CH_2$)-Ph |
| 3-1222 | Me | 2 | H | 4-[Mor-CO-$(CH_2)_2$]-Ph |
| 3-1223 | Me | 2 | H | 3-[Mor-CO-$(CH_2)_2$]-Ph |
| 3-1224 | Me | 2 | H | 3-$Me_2N$-Ph |
| 3-1225 | Me | 2 | H | 4-($Me_2N$-$CH_2$)-Ph |
| 3-1226 | Me | 2 | H | 3-($Me_2N$-$CH_2$)-Ph |
| 3-1227 | Me | 2 | H | 4-[$Me_2N$-$(CH_2)_2$]-Ph |
| 3-1228 | Me | 2 | H | 3-[$Me_2N$-$(CH_2)_2$]-Ph |
| 3-1229 | Me | 2 | H | 4-[$Me_2N$-$(CH_2)_3$]-Ph |
| 3-1230 | Me | 2 | H | 3-[$Me_2N$-$(CH_2)_3$]-Ph |
| 3-1231 | Me | 2 | H | 4-Mor-Ph |

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|---|---|---|---|---|
| 3-1232 | Me | 2 | H | 3-Mor-Ph |
| 3-1233 | Me | 2 | H | 4-(Mor-$CH_2$)-Ph |
| 3-1234 | Me | 2 | H | 3-(Mor-$CH_2$)-Ph |
| 3-1235 | Me | 2 | H | 4-[Mor-$(CH_2)_2$]-Ph |
| 3-1236 | Me | 2 | H | 3-[Mor-$(CH_2)_2$]-Ph |
| 3-1237 | Me | 2 | H | 4-[Mor-$(CH_2)_3$]-Ph |
| 3-1238 | Me | 2 | H | 3-[Mor-$(CH_2)_3$]-Ph |
| 3-1239 | Me | 2 | H | 4-Pipo-Ph |
| 3-1240 | Me | 2 | H | 3-Pipo-Ph |
| 3-1241 | Me | 2 | H | 4-(Pipo-$CH_2$)-Ph |
| 3-1242 | Me | 2 | H | 3-(Pipo-$CH_2$)-Ph |
| 3-1243 | Me | 2 | H | 4-[Pipo-$(CH_2)_2$]-Ph |
| 3-1244 | Me | 2 | H | 3-[Pipo-$(CH_2)_2$]-Ph |
| 3-1245 | Me | 2 | H | 4-[Pipo-$(CH_2)_3$]-Ph |
| 3-1246 | Me | 2 | H | 3-[Pipo-$(CH_2)_3$]-Ph |
| 3-1247 | Me | 2 | H | 4-HO-Ph |
| 3-1248 | Me | 2 | H | 3-HO-Ph |
| 3-1249 | Me | 2 | H | 4-(HO-$CH_2$)-Ph |
| 3-1250 | Me | 2 | H | 3-(HO-$CH_2$)-Ph |
| 3-1251 | Me | 2 | H | 4-[HO-$(CH_2)_2$]-Ph |
| 3-1252 | Me | 2 | H | 3-[HO-$(CH_2)_2$]-Ph |
| 3-1253 | Me | 2 | H | 4-[HO-$(CH_2)_3$]-Ph |
| 3-1254 | Me | 2 | H | 3-[HO-$(CH_2)_3$]-Ph |
| 3-1255 | Me | 2 | H | 4-[MeCH(OH)]-Ph |
| 3-1256 | Me | 2 | H | 3-[MeCH(OH)]-Ph |
| 3-1257 | Me | 2 | H | 4-[MeCH(OH)-$CH_2$]-Ph |
| 3-1258 | Me | 2 | H | 3-[MeCH(OH)-$CH_2$]-Ph |

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|---|---|---|---|---|
| 3-1259 | Me | 2 | H | 4-[MeCH(OH)-$(CH_2)_2$]-Ph |
| 3-1260 | Me | 2 | H | 3-[MeCH(OH)-$(CH_2)_2$]-Ph |
| 3-1261 | Me | 2 | H | 3-CN-Ph |
| 3-1262 | Me | 2 | H | 4-(CN-$CH_2$)-Ph |
| 3-1263 | Me | 2 | H | 3-(CN-$CH_2$)-Ph |
| 3-1264 | Me | 2 | H | 4-[CN-$(CH_2)_2$]-Ph |
| 3-1265 | Me | 2 | H | 3-[CN-$(CH_2)_2$]-Ph |
| 3-1266 | Me | 2 | H | 3-Ac-Ph |
| 3-1267 | Me | 2 | H | 4-(Ac-$CH_2$)-Ph |
| 3-1268 | Me | 2 | H | 3-(Ac-$CH_2$)-Ph |
| 3-1269 | Me | 2 | H | 4-[Ac-$(CH_2)_2$]-Ph |
| 3-1270 | Me | 2 | H | 3-[Ac-$(CH_2)_2$]-Ph |
| 3-1271 | Me | 2 | H | 4-($CF_3$CO)-Ph |
| 3-1272 | Me | 2 | H | 4-(EtCO)-Ph |
| 3-1273 | Me | 2 | H | 3-(EtCO)-Ph |
| 3-1274 | Me | 2 | H | 4-(EtCO-$CH_2$)-Ph |
| 3-1275 | Me | 2 | H | 3-(EtCO-$CH_2$)-Ph |
| 3-1276 | Me | 2 | H | 4-[EtCO-$(CH_2)_2$]-Ph |
| 3-1277 | Me | 2 | H | 3-[EtCO-$(CH_2)_2$]-Ph |
| 3-1278 | Me | 2 | H | 4-(iPrCO)-Ph |
| 3-1279 | Me | 2 | H | 4-(cBuCO)-Ph |
| 3-1280 | Me | 2 | H | 4-(cPrCO)-Ph |
| 3-1281 | Me | 2 | H | 4-(Ph-CO)-Ph |
| 3-1282 | Me | 2 | H | 4-Ac-3-MeO-Ph |
| 3-1283 | Me | 2 | H | 4-Ac-3-OH-Ph |
| 3-1284 | Me | 2 | H | 4-Ac-3-Cl-Ph |
| 3-1285 | Me | 2 | H | 4-[$CH_3$C(=N-OH)]-Ph |

| | | | | |
|---|---|---|---|---|
| 3-1286 | Me | 2 | H | 3-[$CH_3C$(=N-OH)]-Ph |
| 3-1287 | Me | 2 | H | 4-[$CH_3C$(=N-OH)-$CH_2$]-Ph |
| 3-1288 | Me | 2 | H | 3-[$CH_3C$(=N-OH)-$CH_2$]-Ph |
| 3-1289 | Me | 2 | H | 4-[$CH_3C$(=N-OH)-$(CH_2)_2$]-Ph |
| 3-1290 | Me | 2 | H | 3-[$CH_3C$(=N-OH)-$(CH_2)_2$]-Ph |
| 3-1291 | Me | 2 | H | 4-[$CH_3C$(=N-OMe)]-Ph |
| 3-1292 | Me | 2 | H | 3-[$CH_3C$(=N-OMe)]-Ph |
| 3-1293 | Me | 2 | H | 4-[$CH_3C$(=N-OMe)-$CH_2$]-Ph |
| 3-1294 | Me | 2 | H | 3-[$CH_3C$(=N-OMe)-$CH_2$]-Ph |
| 3-1295 | Me | 2 | H | 4-[$CH_3C$(=N-OMe)-$(CH_2)_2$]-Ph |
| 3-1296 | Me | 2 | H | 3-[$CH_3C$(=N-OMe)-$(CH_2)_2$]-Ph |
| 3-1297 | Me | 2 | H | 4-($Me_2NSO_2$)-Ph |
| 3-1298 | Me | 2 | H | 4-[$(MeO)_2CH$]-Ph |
| 3-1299 | Me | 2 | H | 3-[$(MeO)_2CH$]-Ph |
| 3-1300 | Me | 2 | H | 4-[$(MeO)_2CH$-$CH_2$]-Ph |
| 3-1301 | Me | 2 | H | 3-[$(MeO)_2CH$-$CH_2$]-Ph |
| 3-1302 | Me | 2 | H | 4-[$(MeO)_2CH$-$(CH_2)_2$]-Ph |
| 3-1303 | Me | 2 | H | 3-[$(MeO)_2CH$-$(CH_2)_2$]-Ph |
| 3-1304 | Me | 2 | H | 4-[$Me(MeO)_2C$]-Ph |
| 3-1305 | Me | 2 | H | 3-[$Me(MeO)_2C$]-Ph |
| 3-1306 | Me | 2 | H | 4-[$Me(MeO)_2C$-$CH_2$]-Ph |
| 3-1307 | Me | 2 | H | 3-[$Me(MeO)_2C$-$CH_2$]-Ph |
| 3-1308 | Me | 2 | H | 4-[$Me(MeO)_2C$-$(CH_2)_2$]-Ph |
| 3-1309 | Me | 2 | H | 3-[$Me(MeO)_2C$-$(CH_2)_2$]-Ph |
| 3-1310 | Me | 2 | H | 4-[$(EtO)_2CH$]-Ph |
| 3-1311 | Me | 2 | H | 3-[$(EtO)_2CH$]-Ph |
| 3-1312 | Me | 2 | H | 4-[$(EtO)_2CH$-$CH_2$]-Ph |

| | | | | |
|---|---|---|---|---|
| 3-1313 | Me | 2 | H | 3-[$(EtO)_2CH$-$CH_2$]-Ph |
| 3-1314 | Me | 2 | H | 4-[$(EtO)_2CH$-$(CH_2)_2$]-Ph |
| 3-1315 | Me | 2 | H | 3-[$(EtO)_2CH$-$(CH_2)_2$]-Ph |
| 3-1316 | Me | 2 | H | 4-[$Me(EtO)_2C$]-Ph |
| 3-1317 | Me | 2 | H | 3-[$Me(EtO)_2C$]-Ph |
| 3-1318 | Me | 2 | H | 4-[$Me(EtO)_2C$-$CH_2$]-Ph |
| 3-1319 | Me | 2 | H | 3-[$Me(EtO)_2C$-$CH_2$]-Ph |
| 3-1320 | Me | 2 | H | 4-[$Me(EtO)_2C$-$(CH_2)_2$]-Ph |
| 3-1321 | Me | 2 | H | 3-[$Me(EtO)_2C$-$(CH_2)_2$]-Ph |
| 3-1322 | Me | 2 | H | 4-(2-Dioxo)-Ph |
| 3-1323 | Me | 2 | H | 3-(2-Dioxo)-Ph |
| 3-1324 | Me | 2 | H | 4-[(2-Dioxo)-$CH_2$]-Ph |
| 3-1325 | Me | 2 | H | 3-[(2-Dioxo)-$CH_2$]-Ph |
| 3-1326 | Me | 2 | H | 4-[(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-1327 | Me | 2 | H | 3-[(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-1328 | Me | 2 | H | 4-[2-Me-(2-Dioxo)]-Ph |
| 3-1329 | Me | 2 | H | 3-[2-Me-(2-Dioxo)]-Ph |
| 3-1330 | Me | 2 | H | 4-[2-Me-(2-Dioxo)-$CH_2$]-Ph |
| 3-1331 | Me | 2 | H | 3-[2-Me-(2-Dioxo)-$CH_2$]-Ph |
| 3-1332 | Me | 2 | H | 4-[2-Me-(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-1333 | Me | 2 | H | 3-[2-Me-(2-Dioxo)-$(CH_2)_2$]-Ph |
| 3-1334 | Me | 2 | H | 4-(2-Dioxa)-Ph |
| 3-1335 | Me | 2 | H | 3-(2-Dioxa)-Ph |
| 3-1336 | Me | 2 | H | 4-[(2-Dioxa)-$CH_2$]-Ph |
| 3-1337 | Me | 2 | H | 3-[(2-Dioxa)-$CH_2$]-Ph |
| 3-1338 | Me | 2 | H | 4-[(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-1339 | Me | 2 | H | 3-[(2-Dioxa)-$(CH_2)_2$]-Ph |

| | | | | |
|---|---|---|---|---|
| 3-1340 | Me | 2 | H | 4-[2-Me-(2-Dioxa)]-Ph |
| 3-1341 | Me | 2 | H | 3-[2-Me-(2-Dioxa)]-Ph |
| 3-1342 | Me | 2 | H | 4-[2-Me-(2-Dioxa)-$CH_2$]-Ph |
| 3-1343 | Me | 2 | H | 3-[2-Me-(2-Dioxa)-$CH_2$]-Ph |
| 3-1344 | Me | 2 | H | 4-[2-Me-(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-1345 | Me | 2 | H | 3-[2-Me-(2-Dioxa)-$(CH_2)_2$]-Ph |
| 3-1346 | Me | 2 | H | 2-Me-1-oxo-5-IIndn |
| 3-1347 | Me | 2 | H | 6-BzOxaz |
| 3-1348 | Me | 2 | H | 4-(HO-N=)-7-Chr |
| 3-1349 | Me | 2 | H | 3-Me-6-BzIox |
| 3-1350 | Me | 2 | H | 2-Me-6-BzOxaz |
| 3-1351 | Me | 2 | H | 2-Me-5-BzOxaz |
| 3-1352 | Me | 2 | H | 2,3-dihydro-5-BzFur |
| 3-1353 | Me | 2 | H | 6-Qui |
| 3-1354 | Me | 2 | H | 6-Iqui |
| 3-1355 | Me | 2 | H | 3-(HO-N=)-2,3-dihydro-6-BzFur |
| 3-1356 | Me | 2 | H | 2-Me-6-BzThaz |
| 3-1357 | Me | 2 | H | 5-Ind |
| 3-1358 | Me | 2 | H | 4-Ac-2-Thaz |
| 3-1359 | Me | 2 | H | 5-Ac-2-Thi |
| 3-1360 | Me | 2 | H | 5-Ac-2-Fur |
| 3-1361 | Me | 2 | H | 5-$Me_2$NCO-2-Py |
| 3-1362 | Me | 2 | H | 5-($Me_2$NCO-$CH_2$)-2-Py |
| 3-1363 | Me | 2 | H | 5-[$Me_2$NCO-$(CH_2)_2$]-2-Py |
| 3-1364 | Me | 2 | H | 4-$Me_2$NCO-2-Thaz |
| 3-1365 | Me | 2 | H | 5-$Me_2$NCO-2-Thaz |
| 3-1366 | Me | 2 | H | 4-($Me_2$NCO-$CH_2$)-2-Thaz |

| | | | | |
|---|---|---|---|---|
| 3-1367 | Me | 2 | H | 5-($Me_2NCO$-$CH_2$)-2-Thaz |
| 3-1368 | Me | 2 | H | 2-Thazn |
| 3-1369 | Me | 2 | H | 2-Oxazn |

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The compounds which are preferred in the above Table 1 to Table 3 for exemplified compounds are the exemplified compounds designated as numbers 1-7, 1-16, 1-17, 1-20, 1-21, 1-22, 1-23, 1-27, 1-28, 1-29, 1-36, 1-39, 1-40, 1-44, 1-68, 1-95, 1-96, 1-97, 1-99, 1-100, 1-101, 1-102, 1-105, 1-109, 1-112, 1-115, 1-118, 1-123, 1-133, 1-139, 1-140, 1-141, 1-143, 1-144, 1-146, 1-149, 1-152, 1-155, 1-156, 1-157, 1-164, 1-173, 1-181, 1-182, 1-183, 1-190, 1-229, 2-33, 2-102, 3-22, 3-30, 3-86, 3-87, 3-88, 3-89, 3-97, 3-98, 3-99, 3-100, 3-104, 3-105, 3-106, 3-107, 3-110, 3-111, 3-112, 3-116, 3-117, 3-123, 3-124, 3-125, 3-127, 3-131, 3-132, 3-136, 3-138, 3-139, 3-140, 3-142, 3-143, 3-161, 3-182, 3-429, 3-430, 3-431, 3-432, 3-876, 3-886, 3-894, 3-912, 3-918, 3-924, 3-925, 3-927, 3-934, 3-940, 3-946, 3-952, 3-970, 3-979, 3-1003, 3-1004, 3-1005, 3-1007, 3-1018, 3-1019, 3-1023, 3-1030, 3-1031, 3-1032, 3-1034, 3-1035, 3-1037, 3-1043, 3-1082, 3-1098, 3-1099, 3-1100, 3-1101, 3-1102, 3-1103, 3-1104, 3-1105, 3-1107, 3-1108, 3-1109, 3-1110, 3-1111, 3-1112, 3-1113, 3-1116, 3-1117, 3-1118 and 3-1120, and more preferred compounds are the exemplified compounds designated as numbers 1-17, 1-21, 1-22, 1-28, 1-29, 1-68, 1-99, 1-101, 1-102, 1-105, 1-109, 1-112, 1-115, 1-123, 1-143, 1-144, 1-146, 1-152, 1-155, 1-157, 1-164, 1-229, 3-30, 3-86, 3-87, 3-88, 3-99, 3-100, 3-104, 3-106, 3-107, 3-111, 3-116, 3-124, 3-127, 3-136, 3-142, 3-143, 3-161, 3-182, 3-429, 3-430, 3-876, 3-924, 3-925, 3-927, 3-934, 3-940, 3-952, 3-970, 3-979, 3-1003, 3-1004, 3-1005, 3-1007, 3-1018, 3-1019, 3-1031, 3-1034, 3-1035, 3-1037, 3-1043, 3-1082, 3-1098, 3-1099, 3-1100, 3-1101, 3-1102, 3-1104, 3-1110, 3-1111, 3-1113, 3-1116 and 3-1117.

Of these, particularly preferred compounds are

· 3-amino-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 1-21),

· 3-amino-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]-6-methylthieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 1-68),

· 3-amino-4-{3-[3-(2-hydroxyethoxy)propyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 1-101),

· 3-amino-4-{(3S)-[(2-methoxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide hydrochloride (exemplary compound No. 1-112),

· 3-amino-4-{(3S)-3-[(3-methoxypropoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 1-115),

· 3-amino-4-(3-{[2-(dimethylamino)-2-oxoethoxy]methyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 1-155),

· 3-amino-4-(3-{3-[2-(dimethylamino)-2-oxoethoxy]propyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 1-157),

· 4-[4-(4-acetylphenyl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-99),

· 3-amino-4-[4-(4-propionylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-100),

· 3-amino-4-{4-[4-(dimethylamino)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-104),

· 3-amino-4-(4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-107),

· 4-[4-(5-acetylpyridin-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-142),

· 3-amino-4-(4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepan-1-yl)-6-methylthieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-182),

· 3-amino-4-{4-[4-(2-methoxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-876),

· 3-amino-4-(4-{4-[2-(dimethylamino)-2-oxoethyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-925),

· 3-amino-4-(4-{4-[3-(dimethylamino)-2-oxopropyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-927),

· 3-amino-4-{4-[4-(azetidin-1-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-940),

· 3-amino-4-{4-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[2-(dimethylamino)ethyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-979),

· 3-amino-4-{4-[4-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1003),

· 3-amino-4-{4-[3-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1004),

· 3-amino-4-{4-[4-(3-hydroxypropyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1005),

· 3-amino-4-{4-[4-(1-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1007),

· 3-amino-4-{4-[4-(2-oxopropyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1019),

· 3-amino-4-(4-{4-[(1E)-N-hydroxyethaneimidoyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1037),

· 3-amino-4-(4-{4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1082),

· 3-amino-4-[4-(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1098),

· 3-amino-4-[4-(1,3-benzoxazol-6-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1099),

· 3-amino-4-{4-[(4E)-4-(hydroxyimino)-3,4-dihydro-2H-chromen-7-yl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1100),

· 4-[4-(4-acetyl-1,3-thiazol-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1110),

· 4-[4-(5-acetylthiophen-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1111), and

· 3-amino-4-(4-{4-[(dimethylamino)carbonyl]-1,3-thiazol-2-yl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (exemplary compound No. 3-1116)

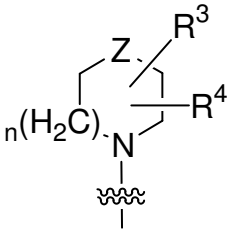
or pharmacologically acceptable salts thereof.

Embodiments of the Invention

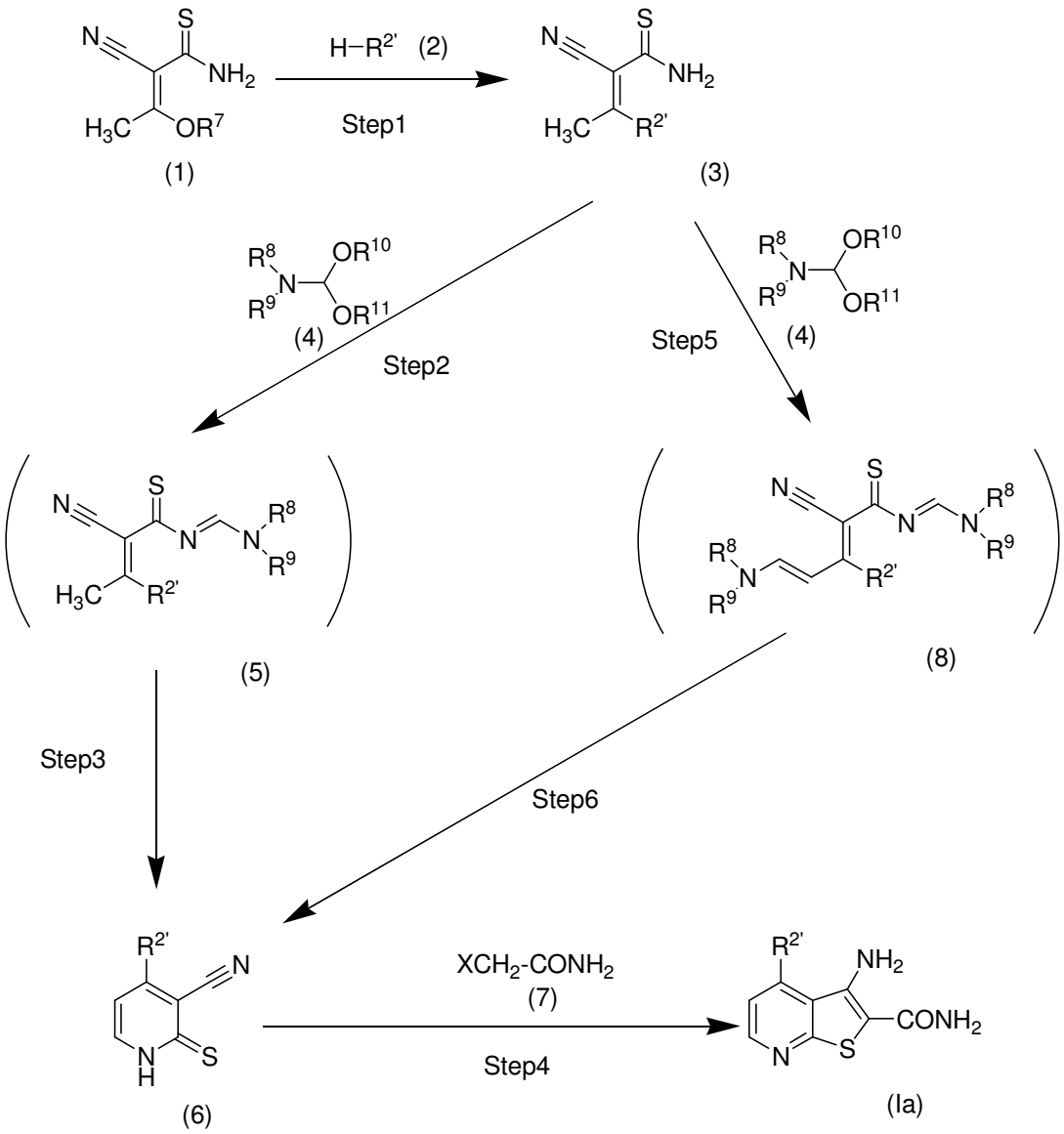
The compounds having a general formula (I) of the present invention can be produced by the processes mentioned below.

<Process A>

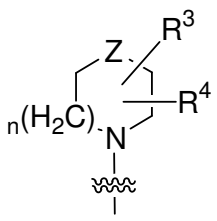
The compound wherein $R^1$ is a hydrogen atom; $R^2$ is a group $R^aNH$-, $R^a(R^b)N$- or



in general formula (I) can be produced according to Process A.




[wherein $R^{2'}$ represents a group $R^aNH$-, $R^a(R^b)N$- or



in the definition of $R^2$,

$R^7$ represents methyl or ethyl,

$R^8$ and $R^9$ independently represent a $C_1$-$C_6$ alkyl group (preferably methyl, ethyl or isopropyl, particularly preferably methyl) or they together with the nitrogen atom to which they are bonded represent a 4- to 7-membered heterocyclyl group which contains 1 to 2 sulfur, oxygen and/or nitrogen atoms (preferably pyrrolidinyl, piperidyl, morpholinyl), and

$R^{10}$ and $R^{11}$ independently represent a $C_1$-$C_6$ alkyl group (preferably methyl, ethyl or isopropyl, particularly preferably methyl), and

X represents a halogen atom (preferably a chlorine atom or a bromine atom, particularly preferably a chlorine atom)].

Step 1 is a step for reacting compound (1) and amine compound (2) in an inert solvent to produce compound (3), and it can be carried out following a method described in J. Org. Chem, (1962) 27, 2433-2439.

The inert solvent to be used is, for example, an alcohol such as methanol, ethanol, propanol, 2-propanol or butanol; an aromatic hydrocarbon such as benzene, toluene or xylene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane; an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or hexamethylphosphorotriamide; or a halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, m-dichlorobenzene, fluorobenzene, trichloromethylbenzene or trifluoromethyl benzene, and preferably it is methanol, ethanol or N,N-dimethylformamide.

Reaction temperature varies depending on the raw material compounds or solvent used, but it is usually 0°C to reflux temperature of the reaction mixture and preferably it is room temperature to reflux temperature of the reaction mixture.

Reaction time differs according to the raw material compounds, solvent or reaction temperature used, but it is usually from 30 minutes to 96 hours, preferably from 30 minutes to 24 hours.

The deposit obtained by filtering the reaction liquid or the residue obtained by evaporating the solvent after the reaction terminates can be used in the next step (Step 2) without being particularly purified. In addition, the reaction solution can be used as it is in the next step when an amide is used as inert solvent.

Step 2 is a step for reacting compound (3) and N,N-dialkylformamide dialkyl acetal (4) in an inert solvent to produce amidine derivative (5).

The inert solvent to be used is, for example, an alcohol such as methanol, ethanol, propanol, 2-propanol or butanol; an aromatic hydrocarbon such as benzene, toluene or xylene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane; an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or hexamethylphosphorotriamide; or a halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, m-dichlorobenzene, fluorobenzene, trichloromethylbenzene or trifluoromethyl benzene, and preferably it is ethanol or N,N-dimethylformamide.

The amount of N,N-dialkylformamide dialkyl acetal (4) used for the reaction is preferably 1 to 2 equivalent for one equivalent of compound (3).

Reaction temperature varies depending on the raw material compounds or solvent used, but it is usually 0°C to reflux temperature of the reaction mixture, and preferably it is room temperature.

Reaction time differs according to the raw material compounds, solvent or reaction temperature used, but it is usually from 30 minutes to 96 hours, preferably from 30 minutes to 24 hours.

The deposit obtained by filtering the reaction liquid or the residue obtained by evaporating the solvent after the reaction terminates can be used in the next step (Step 3) without being particularly purified. In addition, the reaction solution can be used as it is in the next step when an amide is used as inert solvent.

Step 3 is a step for treating amidine derivative (5) in an inert solvent to produce thiopyridone derivatives (6).

The inert solvent to be used is, for example, an alcohol such as methanol, ethanol, propanol, 2-propanol or butanol; an aromatic hydrocarbon such as benzene, toluene or xylene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane; an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or hexamethylphosphorotriamide; or a halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, m-dichlorobenzene, fluorobenzene, trichloromethylbenzene or trifluoromethyl benzene, preferably it is ethanol or N,N-dimethylformamide, and particularly preferably it is N,N-dimethylformamide.

Reaction temperature varies depending on the raw material compounds or solvent used, but it is usually room temperature to reflux temperature of the reaction mixture and preferably it is 50°C to 120°C.

Reaction time differs according to the by raw material compounds, solvent or reaction temperature used, but it is usually from 10 minutes to six hours, preferably from 10 minutes to two hours.

After the reaction terminates, the object compound is collected from the reaction mixture according to a conventional method (extraction, column chromatography, filtration and concentration) as required. In addition, the reaction

solution can be used as it is in the next step (Step 4) when an amide is used as inert solvent.

Step 4 is a step for reacting thiopyridone derivative (6) and α-haloacetamide (7) in the presence of a base in an inert solvent to produce thienopyridine derivatives (Ia).

The inert solvent to be used is, for example, an alcohol such as methanol, ethanol, propanol, 2-propanol or butanol; or an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or hexamethylphosphorotriamide, and preferably it is ethanol or N,N-dimethylformamide.

The base to be used is, for example, an organic base such as triethylamine or 1,8-diazabicyclo[5.4.0]-7-undecene (DBU); an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium tert-butoxide or lithium methoxide; an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide; or an aqueous solution of an alkali metal hydroxide, and preferably it is 1,8-diazabicyclo[5.4.0]-7-undecene (DBU), sodium ethoxide or an aqueous solution of sodium hydroxide.

Reaction temperature varies depending on the raw material compounds, solvent or base used, but it is usually 0°C to reflux temperature of the reaction mixture and preferably it is room temperature to reflux temperature of the reaction mixture.

Reaction time differs according to the raw material compounds, solvent, base or reaction temperature used, but it is usually from 10 minutes to six hours, preferably from 30 minutes to two hours.

After the reaction terminates, the object compound is collected from the reaction mixture according to a conventional method as required.

For example, the object compound can be obtained by adding water to the reaction mixture and filtering the separated object compound; or after neutralizing the reaction mixture appropriately and removing by filtration insolubles if present, adding water, extracting with a water-immiscible organic solvent such as ethyl acetate or toluene and washing with water and the like, and evaporating the solvent after drying over anhydrous magnesium sulfate and the like.

If necessary, the obtained compound can be separated and purified by a conventional method, for example by silica gel column chromatography.

Step 5 is a step for reacting compound (3) and N,N-dialkylformamide dialkyl acetal (4) in an inert solvent to produce amidine derivative (8).

The inert solvent to be used is, for example, an alcohol such as methanol, ethanol, propanol, 2-propanol or butanol; an aromatic hydrocarbon such as benzene, toluene or xylene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane; an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or hexamethylphosphorotriamide; or a halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, m-dichlorobenzene, fluorobenzene, trichloromethylbenzene or trifluoromethyl benzene, preferably it is an aromatic hydrocarbon, and particularly preferably it is toluene.

The amount of N,N-dialkylformamide dialkyl acetal (4) used for the reaction is preferably 2 to 3 equivalents for one equivalent of compound (3).

Reaction temperature varies depending on the raw material compounds or solvent used, but it is usually 0°C to reflux temperature of the reaction mixture and preferably it is room temperature to reflux temperature of the reaction mixture.

Reaction time is differs according to the raw material compounds, solvent or reaction temperature used, but it is usually from three minutes to six hours, preferably from three minutes to two hours.

The residue obtained by evaporating the solvent under reduced pressure after the reaction terminates can be used in the next step (Step 6) without being particularly purified.

Step 6 is a step for treating amidine derivative (8) with an alkaline aqueous solution to produce thiopyridone derivatives (6).

The alkaline aqueous solution to be used is, for example, an aqueous solution of an alkali metal hydroxide (for example, sodium hydroxide, potassium hydroxide or lithium hydroxide) and preferably an aqueous solution of sodium hydroxide.

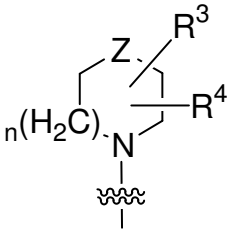
Reaction temperature varies depending on the raw material compounds or solvent used, but it is usually room temperature to reflux temperature of the reaction mixture and preferably it is reflux temperature of the reaction mixture.

Reaction time differs according to the raw material compounds, solvent or reaction temperature used, but it is usually from 10 minutes to two hours, preferably from 30 minutes to one hour.

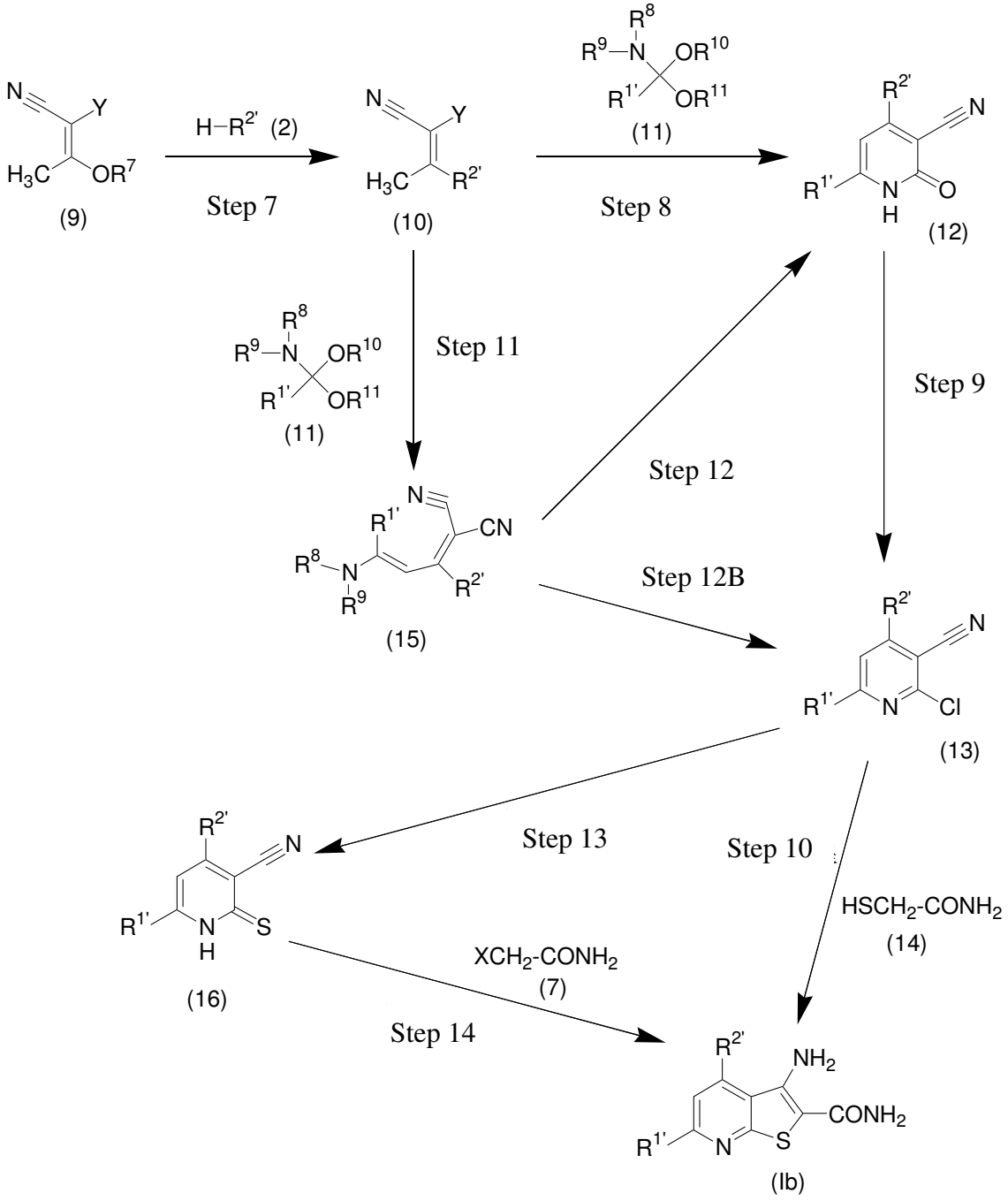
After the reaction terminates, the object compound is collected from the reaction mixture according to a conventional method (extraction, column chromatography, filtration and concentration) as required.

<Process B>

The compound wherein $R^1$ is a $C_1$-$C_6$ alkyl group; $R^2$ is a group $R^aNH$-, $R^a(R^b)N$- or



in general formula (I) can be produced according to Process B.




(wherein $R^{2'}$, $R^8$, $R^9$, $R^{10}$, $R^{11}$ and X represent the same as defined above, and $R^{1'}$ represents a $C_1$-$C_6$ alkyl group in the definition of $R^1$, and Y represents $CONH_2$ or CN.)

Step 7 is a step for reacting compound (9) and amine compound (2) in an inert solvent to produce compound (10), and it can be carried out following a similar method as described in Step 1.

Step 8 is a step for reacting a compound (10) in which Y is $CONH_2$ and (N-N-dialkyl)alkylamide dialkyl acetal (11) in an inert solvent to produce pyridone derivative (12), and it can be carried out following a method described in Pharm. Chem. J. (Engl. Transl.) 25, (1991), 623-628.

The inert solvent to be used is, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; or an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or hexamethylphosphorotriamide, and preferably it is an amide and particularly preferably it is N,N-dimethylformamide.

Reaction temperature varies depending on the raw material compounds or solvent used, but it is usually room temperature to reflux temperature of the reaction mixture and preferably it is 50°C to reflux temperature of the reaction mixture.

Reaction time differs according to the raw material compounds, solvent or reaction temperature used, but it is usually from one hour to 24 hours, preferably from one hour to five hours.

After the reaction terminates, the object compound is collected from the reaction mixture according to a conventional method as required.

For example, the object compound can be obtained by neutralizing the reaction mixture appropriately and removing by filtration insolubles if present, adding water, extracting with a water-immiscible organic solvent such as ethyl acetate or toluene and washing with water and the like, and evaporating the solvent after drying over anhydrous magnesium sulfate and the like.

If necessary, the obtained compound can be separated and purified by a conventional method, for example by silica gel column chromatography.

Step 9 is a step for halogenating pyridone derivative (12) in the presence of a base with a halogenating agent to produce chloropyridine derivative (13).

When the reaction is carried out in an inert solvent, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; or an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane, and preferably toluene or dioxane, is used as solvent.

The base to be used can be, for example, an organic amine such as triethylamine, tributylamine, diisopropylethylamine, N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]-7-undecene (DBU), and particularly preferably N,N-dimethylaniline.

The halogenating agent to be used can be, for example, a phosphorus chloride such as phosphorus trichloride, phosphorous pentachloride or phosphorus oxychloride; or thionyl chloride, and preferably it is phosphorous pentachloride, phosphorus oxychloride or thionyl chloride.

Reaction temperature varies depending on the raw material compounds, solvent, base or halogenating agent, but it is usually room temperature to reflux temperature of the reaction mixture, and preferably it is 50°C to reflux temperature of the reaction mixture.

Reaction time differs according to the raw material compounds, solvent, base, halogenating agent or reaction temperature, but it is usually from one hour to 24 hours, preferably from one hour to eight hours.

After the reaction terminates, the object compound is collected from the reaction mixture according to a conventional method as required.

For example, the object compound can be obtained by neutralizing the reaction mixture appropriately and removing by filtration insolubles if present, adding water, extracting with a water-immiscible organic solvent such as ethyl acetate or toluene and washing with water and the like, and evaporating the solvent after drying over anhydrous magnesium sulfate and the like.

If necessary, the obtained compound can be separated and purified by a conventional method, for example by silica gel column chromatography.

Step 10 is a step for reacting chloropyridine derivative (13) and 2-mercaptoacetamide (14) in the presence of a base in an inert solvent to produce thienopyridine derivative (Ib).

The inert solvent to be used is, for example, an alcohol such as methanol, ethanol, propanol, 2-propanol or butanol; an aromatic hydrocarbon such as benzene, toluene or xylene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane; or an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or hexamethylphosphorotriamide, preferably it is an alcohol or an amide and more preferably it is ethanol or N,N-dimethylformamide.

The base to be used is, for example, an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium tert-butoxide or lithium methoxide; an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide; or an aqueous solution of an alkali metal hydroxide, and preferably it is sodium ethoxide or an aqueous solution of sodium hydroxide.

Reaction temperature varies depending on the raw material compounds, solvent or base used, but it is usually room temperature to reflux temperature of the reaction mixture.

Reaction time differs according to the raw material compounds, solvent, base or reaction temperature used, but it is usually from one hour to 24 hours, preferably from one hour to two hours.

After the reaction terminates, the object compound is collected from the reaction mixture according to a conventional method as required.

For example, the object compound can be obtained by neutralizing the reaction mixture appropriately and removing by filtration insolubles if present, adding water, extracting with a water-immiscible organic solvent such as ethyl acetate or toluene and washing with water and the like, and evaporating the solvent after drying over anhydrous magnesium sulfate and the like.

If necessary, the obtained compound can be separated and purified by a conventional method, for example by silica gel column chromatography.

In addition, 2-mercaptoacetamide (14) can also be generated in the reaction system using 2-(acetylthio)acetamide.

Step 11 is a step for reacting a compound (10) in which Y is CN and (N,N-dialkyl)alkylamide dialkyl acetal (11) in an inert solvent to produce enamine derivative (15).

The inert solvent to be used is, for example, an alcohol such as methanol or ethanol; an aromatic hydrocarbon such as benzene, toluene or xylene; or an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or hexamethylphosphorotriamide, preferably it is an alcohol or an aromatic hydrocarbon, and particularly preferably it is ethanol, toluene or xylene.

Reaction temperature varies depending on the raw material compounds or solvent used, but it is usually room temperature to reflux temperature of the reaction mixture and preferably it is 100°C to reflux temperature of the reaction mixture.

Reaction time differs according to the raw material compounds, solvent or reaction temperature used, but it is usually from one hour to 24 hours, preferably from one hour to eight hours.

After the reaction terminates, the object compound is collected according to a conventional method as required from the reaction mixture.

For example, the object compound can be obtained by neutralizing the reaction mixture appropriately and removing by filtration insolubles if present, adding water, extracting with a water-immiscible organic solvent such as ethyl acetate or toluene and washing with water and the like, and evaporating the solvent after drying over anhydrous magnesium sulfate and the like.

If necessary, the obtained compound can be separated and purified by a conventional method, for example by silica gel column chromatography.

Step 12 is a step for treating enamine derivative (15) with an acid to produce pyridone (12).

The acid to be used can be, for example, an organic acid such as formic acid, acetic acid, trifluoroacetic acid or polyphosphoric acid; or an inorganic acid such as hydrochloric acid, and preferably it is acetic acid or polyphosphoric acid.

When the reaction is carried out in an inert solvent, the solvent can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or hexamethylphosphorotriamide; an alcohol such as methanol or ethanol; or water or a mixed solvent of water and a solvent mentioned above, and particularly preferably it is water.

Reaction temperature varies depending on the raw material compounds or acid used, but it is usually room temperature to reflux temperature of the reaction mixture and preferably it is 50°C to reflux temperature of the reaction mixture.

Reaction time differs according to the raw material compounds, acid or reaction temperature used, but it is usually from one hour to 24 hours, preferably from one hour to eight hours.

Step 12B is a step for reacting an halogenating agent and enamine derivative (15) to produce chloropyridine derivative (13).

When the reaction is carried out in an inert solvent, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane; or an alcohol such as methanol, ethanol, propanol, 2-propanol or butanol can be used as solvent, and preferably methanol or ethanol is used.

The halogenating agent to be used can be, for example, a phosphorus chloride such as phosphorus trichloride, phosphorous pentachloride or phosphorus oxychloride; a sulfone chloride such as thionyl chloride; a chlorosilane such as trimethylsilane chloride, t-butyldimethylsilane chloride; an acid chloride such as oxalyl chloride; or an inorganic acid such as hydrochloric acid or hydrobromic acid, and preferably it is thionyl chloride, trimethylsilane chloride or oxalyl chloride.

However, a bromopyridine derivative is obtained when hydrobromic acid is used.

Reaction temperature varies depending on the raw material compounds, solvent or halogenating agent, but it is usually 0°C to reflux temperature of the reaction mixture, and preferably it is room temperature to reflux temperature of the reaction mixture.

Reaction time differs according to the raw material compounds, solvent or halogenating agent, but it is usually from 10 minutes to 24 hours, preferably from 30 minutes to two hours.

After the reaction terminates, the object compound is collected from the reaction mixture according to a conventional method as required.

For example, the object compound can be obtained by neutralizing the reaction mixture appropriately and removing by filtration insolubles if present, adding water, extracting with a water-immiscible organic solvent such as ethyl acetate or toluene and washing with water and the like, and evaporating the solvent after drying over anhydrous magnesium sulfate and the like.

If necessary, the obtained compound can be separated and purified by a conventional method, for example by silica gel column chromatography.

Step 13 is a step for reacting chloropyridine derivative (13) and thiourea or sodium sulfide (preferably thiourea) in an inert solvent to produce thiopyridone derivative (16).

The inert solvent to be used is, for example, an alcohol such as methanol, ethanol, propanol, 2-propanol or butanol; an aromatic hydrocarbon such as benzene, toluene or xylene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane; or a mixture of solvents mentioned above, preferably it is an alcohol, an aromatic hydrocarbon or a mixture of an alcohol and aromatic hydrocarbon, and more preferably it is ethanol, toluene or a mixture of ethanol and toluene.

Reaction temperature varies depending on the raw material compounds or solvent used, but it is usually room temperature to reflux temperature of the reaction mixture and preferably it is 50°C to reflux temperature of the reaction mixture.

Reaction time differs according to the raw material compounds, solvent or reaction temperature used, but it is usually from one hour to 48 hours, preferably from one hour to 24 hours.

After the reaction terminates, the object compound is collected from the reaction mixture according to a conventional method as required.

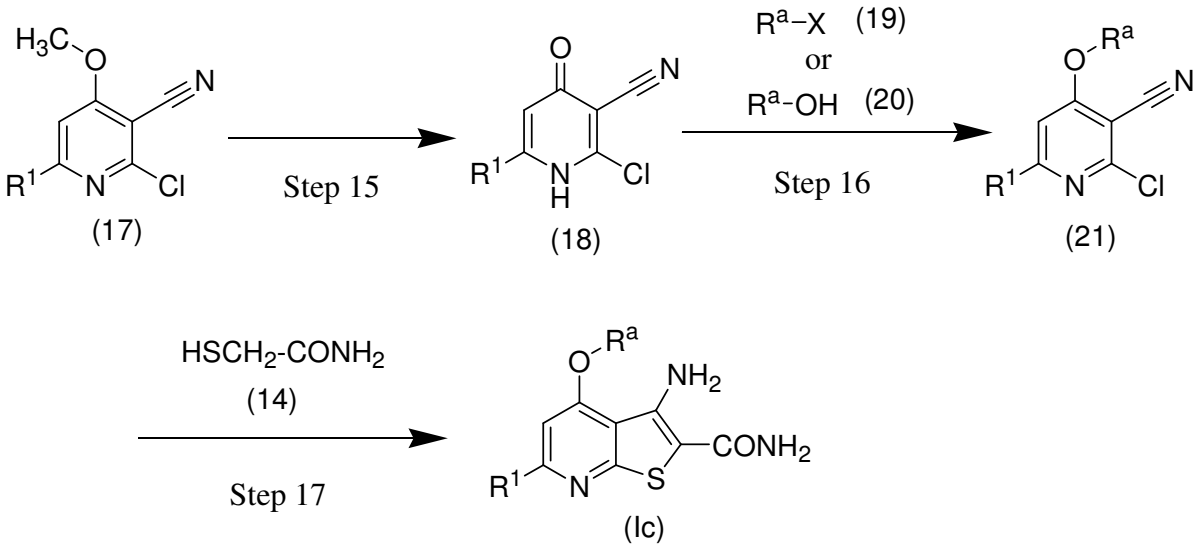
For example, the object compound can be obtained by neutralizing the reaction mixture appropriately and removing by filtration insolubles if present, adding water, extracting with a water-immiscible organic solvent such as ethyl acetate or toluene and washing with water and the like, and evaporating the solvent after drying over anhydrous magnesium sulfate and the like.

If necessary, the obtained compound can be separated and purified by a conventional method, for example by silica gel column chromatography.

Step 14 is a step for reacting thiopyridone derivative (16) and α-haloacetamide (7) in the presence of a base in an inert solvent to produce thienopyridine derivatives (Ib) and can be carried out by a similar method as described in Step 4.

<Process C>

The compound wherein $R^2$ is $R^aO$- in general formula (I) can be produced according to Process C.




(wherein $R^1$, $R^a$ and X represent the same as defined above.)

Step 15 is a step for demethylating methoxypyridine derivative (17) to produce compound (18) and, for example, it can be carried out by heating a methoxypyridine derivative (17) and concentrated hydrochloric acid under reflux in acetic acid solvent.

Step 16 is a step for (a) reacting compound (18) and halogen compound (19) in the presence of a base in an inert solvent or (b) performing a Mitsunobu reaction using compound (18) and alcohol derivative (20), to produce 4-alkoxypyridine derivative (21).

(a) A method using halogen compound (19) (Etherification reaction)

The inert solvent to be used is, for example, an alcohol such as methanol, ethanol, propanol, 2-propanol or butanol; an aromatic hydrocarbon such as benzene, toluene or xylene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane; an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or

hexamethylphosphorotriamide; or a sulfoxide such as dimethylsulfoxide or sulfolane, preferably it is an ether or an amide, and particularly preferably it is tetrahydrofuran or N,N-dimethylacetamide.

The base to be used can be, for example, an alkali metal carbonate such as sodium carbonate or potassium carbonate; an alkali metal hydride such as lithium hydride, sodium hydride or hydrogenation potassium; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium tert-butoxide or lithium methoxide; or an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide, preferably it is an alkali metal carbonate or alkali metal hydride, and more preferably it is potassium carbonate or sodium hydride.

Reaction temperature varies depending on the raw material compounds, solvent or base used, but it is usually 0°C to reflux temperature of the reaction mixture and preferably it is 0°C to room temperature.

Reaction time differs according to the raw material compounds, solvent, base or reaction temperature used, but it is usually from one hour to 48 hours, preferably from one hour to 24 hours.

(b) A method using alcohol derivative (20) (Mitsunobu reaction)

The reaction is usually performed in an inert solvent, and the inert solvent used can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; or an ether such as diethylether, diisopropylether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane, and preferably it is toluene or tetrahydrofuran.

The reagent used for the Mitsunobu reaction is a combination of, for example, an azo compound such as a di($C_1$-$C_6$ alkyl) azodicarboxylate such as diethyl azodicarboxylate or diisopropyl azodicarboxylate or an azodicarbonyl such as 1,1'-(azodicarbonyl)dipiperidine, and a phosphine such as a tri($C_6$-$C_{10}$ aryl)phosphine such as triphenylphosphine or a tri($C_1$-$C_6$ alkyl)phosphine such as tri-n-

butylphosphine, more preferably it is a combination of di($C_1$-$C_6$ alkyl) azodicarboxylate and tri($C_6$-$C_{10}$ aryl)phosphine, and most preferably it is a combination of diethyl azodicarboxylate and triphenylphosphine.

Reaction temperature varies depending on the raw material compounds, solvent or chemical reagent used, but it is usually 0°C to reflux temperature of the solvent and preferably it is 0°C to room temperature.

Reaction time differs according to the raw material compounds, solvent, reagent or reaction temperature used, but it is usually from one hour to 48 hours, preferably from one hour to 24 hours.

After the reaction terminates, the object compound is collected from the reaction mixture according to a conventional method as required.

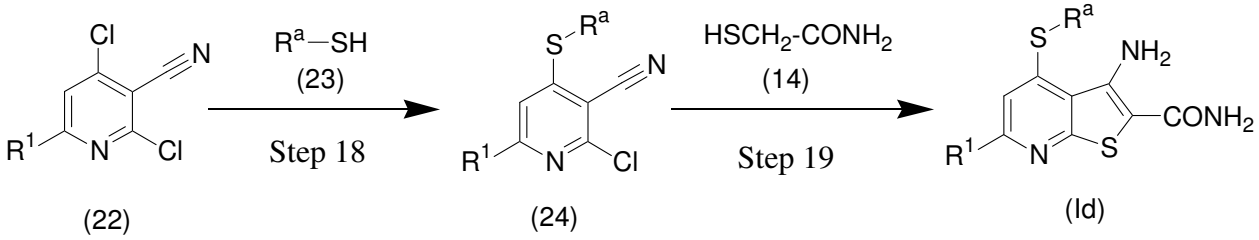
For example, the object compound can be obtained by neutralizing the reaction mixture appropriately and removing by filtration insolubles if present, adding water, extracting with a water-immiscible organic solvent such as ethyl acetate or toluene and washing with water and the like, and evaporating the solvent after drying over anhydrous magnesium sulfate and the like.

If necessary, the obtained compound can be separated and purified by a conventional method, for example by silica gel column chromatography.
It is length of time.

Step 17 is a step for reacting 4-alkoxypyridine derivative (21) and 2-mercaptoacetamide (14) in the presence of a base in an inert solvent to produce thienopyridine derivative (Ic) and it can be carried out by a similar method as described in Step 10.

<Process D>

The compound wherein $R^2$ is $R^aS$- in general formula (I) can be produced according to Process D.




(wherein $R^1$, $R^a$ and X represent the same as defined above.)

Step 18 is a step for reacting dichloropyridine compound (22) and thiol compound (23) or an alkali metal salt thereof (for example, sodium salt) in the presence or absence of a base in an inert solvent to produce 4-alkylthio pyridine derivative (24).

The inert solvent to be used can be, for example, an alcohol such as methanol, ethanol, propanol, 2-propanol or butanol; an aromatic hydrocarbon such as benzene, toluene or xylene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane; an amide such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, N-methylpyrrolidinone or hexamethylphosphorotriamide; or a sulfoxide such as dimethylsulfoxide or sulfolane, preferably it is an ether or an amide, and particularly preferably it is tetrahydrofuran or N,N-dimethylacetamide.

The base to be used can be, for example, an alkali metal hydride such as lithium hydride, sodium hydride or hydrogenation potassium; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium tert-butoxide or lithium methoxide; or an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide, and preferably it is sodium hydride or sodium hydroxide.

Reaction temperature varies depending on the raw material compounds, solvent or base used, but it is usually 0°C to reflux temperature of the reaction mixture and preferably it is 0°C to room temperature.

Reaction time differs according to the raw material compounds, solvent, base or reaction temperature used, but it is usually from one hour to 24 hours, preferably from one hour to six hours.

After the reaction terminates, the object compound is collected from the reaction mixture according to a conventional method as required.

For example, the object compound can be obtained by neutralizing the reaction mixture appropriately and removing by filtration insolubles if present, adding water, extracting with a water-immiscible organic solvent such as ethyl acetate or toluene and washing with water and the like, and evaporating the solvent after drying over anhydrous magnesium sulfate and the like.

If necessary, the obtained compound can be separated and purified by a conventional method, for example by silica gel column chromatography.

In addition, 4-alkoxypyridine derivatives corresponding to compound (24) can be produced by substituting an alcohol derivative (20) for thiol compound (23).

Step 19 is a step for reacting 4-alkylthiopyridine derivative (24) and 2-mercaptoacetamide (14) in the presence of a base in an inert solvent to produce thienopyridine derivative (Id), and it is carried out by a method similar to the method described in Step 10.

Since the compounds having a general formula (I) of the present invention or pharmacologically acceptable salts thereof have effects of promoting osteogenesis, suppressing bone resorption and/or improving bone density, they are useful as a pharmaceutical composition {preferably a pharmaceutical composition for prevention or treatment of osteopathy [for example, osteoporosis (for example, postmenopausal osteoporosis, senile osteoporosis or secondary osteoporosis caused

by use of steroid or immunosuppressant), osteopenia or bone destruction associated with rheumatoid arthritis, Paget's disease of bone, bone fracture or dysostosis due to dwarfism] or osteoarthritis} and can be administered to a mammal (for example, a human, horse, cow or pig, preferably a human) or a bird (preferably a chicken, more preferably a female chicken). The mode for administration can be, for example, oral administration by tablets, capsules, granules, powders or syrup, or parenteral administration by injection or suppository, etc., and preparations for those purposes can be produced by well-known methods using additives such as excipients, lubricants, binders, disintegrants, stabilizing agents, corrigents, diluents.

Excipients can be, for example, organic excipients such as a sugar derivative such as lactose, sucrose, glucose, mannitol or sorbitol, a starch derivative such as corn starch, potato starch, α-starch, dextrin or carboxymethyl starch, a cellulose derivative such as crystalline cellulose, low substituted hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose or internally crosslinked sodium carboxymethyl cellulose, gum arabic, dextran or pullulan; or inorganic excipients such as a silicate derivative such as light anhydrous silicic acid, synthetic aluminium silicate or magnesium aluminometasilicate, a phosphate such as calcium phosphate, a carbonate such as calcium carbonate, or calcium sulphate.

Lubricants can be, for example, stearic acid or a metal stearate such as calcium stearate or magnesium stearate; talc; colloidal silica; wax such as bee gum or spermaceti; boric acid; adipic acid; sulfate such as sodium sulfate; glycol; fumaric acid; sodium benzoate; DL-leucine; sodium salt of fatty acid; a lauryl sulfate such as sodium lauryl sulfate or magnesium lauryl sulfate; silicic acid such as silicic anhydride or silicic acid hydrate; or a starch derivative as mentioned above.

Binders can be, for example, polyvinylpyrrolidone or macrogol or a compound which is similar to the above excipients.

Disintegrants can be, for example, a compound which is similar to the above excipients or a chemically modified starch and/or cellulose such as cross sodium carmellose, sodium carboxymethyl starch or crosslinked polyvinylpyrrolidone.

Stabilizing agents can be, for example, a paraoxybenzoic acid ester such as methylparaben or propylparaben; an alcohol such as chlorobutanol, benzyl alcohol or phenylethyl alcohol; benzalkonium chloride; a phenol such as phenol or cresol; thimerosal; dehydroacetic acid; or sorbic acid.

Corrigents can be, for example, a sweetner, acidulant or flavouring agent usually used.

The amount of the compound having a general formula (I) of the present invention or its pharmacologically acceptable salt varies depending on the symptoms, age, administration method, but it is desirable to administer, for example, 0.0001 mg/kg (preferably, 0.001 mg/kg) for the lower limit and 100 mg/kg (preferably, 10 mg/kg) for the upper limit, in a single dose or divided into multiple doses per day, depending on the symptoms, in the case of oral administration. In the case of intravenous administration, it is desirable to administrate 0.0001 mg/kg (preferably, 0.001 mg/kg) for the lower limit and 1 mg/kg (preferably, 0.1 mg/kg) for the upper limit, in a single dose or divided into multiple doses, per day for an adult depending on the symptoms.

Effects of the Invention

Since the compound having a general formula (I) of the present invention or pharmacologically acceptable salts thereof have effects of promoting osteogenesis, suppressing bone resorption and/or improving bone density, they are useful as a pharmaceutical composition {preferably a pharmaceutical composition for prevention or treatment of osteopathy [for example, osteoporosis (for example, postmenopausal osteoporosis, senile osteoporosis or secondary osteoporosis caused

by the use of steroids or immunosuppressants), osteopenia or bone destruction associated with rheumatoid arthritis, Paget's disease of bone, bone fracture or dysostosis due to dwarfism] or osteoarthritis}.

Best Mode for Carrying out the Invention

The present invention will be described in more detail by way of the Examples, Preparation Examples and Test Examples below but the present invention is not limited to these.

(EXAMPLES)

(Example 1) 3-amino-4-(dimethylamino)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-17)

The compound was produced by the following method with reference to a method described in Pharm.Chem.J.(Engl.Transl.),26,(1992),870-874.

(1a) (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide

Cyanothioacetamide (1.00 g, 10 mmol) and N,N-dimethylacetamide dimethylacetal (1.73 g, 13 mmol) were dissolved in acetonitrile (5 mL) and the mixture was stirred at room temperature for one hour. The deposited crystal was filtered and the crystal was further washed with acetonitrile and 1.05 g (yield 62%) of the title compound was obtained.

Mp 155-158°C;

$^1$H NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.27 (3H, s), 3.03 (6H, s), 8.08 (1H, br), 8.83 (1H, br).

(1b) 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide (1.05 g, 6.2 mmol) produced in Example 1 (1a) and N,N-dimethylformamide dimethylacetal (2.22 g, 18.6 mmol) were dissolved in toluene (10 mL) and the mixture was stirred under heat reflux for two hours. The residue obtained by concentrating the mixture under reduced pressure was suspended in 1N aqueous solution of sodium hydroxide (10

mL) and heated under reflux for 30 minutes. After the reaction mixture was cooled to room temperature, 1N hydrochloric acid (15 mL) was added. The deposited solid was filtered and washed with water and ethanol and 0.87 g (yield 78%) of the title compound was obtained.

Mp 246-250°C;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 3.12 (6H, s), 6.25 (1H, d, J = 7.3 Hz), 7.29-7.33 (1H, m), 12.40 (1H, br).

(1c) 3-amino-4-(dimethylamino)thieno[2,3-b]pyridine-2-carboxamide

8N aqueous solution of sodium hydroxide (2 mL) and 2-chloroacetamide (0.54 g, 5.8 mmol) were added to an N,N-dimethylformamide (10 mL) solution of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (0.87 g) produced in Example 1 (1b), and the mixture was stirred at room temperature for one hour. Water (100 mL) was added to the reaction mixture, and the deposited crystal was filtered and further washed with water and ethanol and 0.79 g (yield 54%) of the title compound was obtained.

Mp 208-211°C;

IR (KBr) $\nu_{max}$ 3430, 3296, 3132, 1673, 1582, 1372, 979 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 2.80 (6H, s), 6.96 (1H, d, J = 5.5 Hz), 6.97 (2H, br), 7.04 (2H, br), 8.36 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 237 $[M+H]^+$;

Anal. Calcd for $C_{10}H_{12}N_4SO$: C, 50.83; H, 5.12; N, 23.71; S, 13.57. Found: C, 50.70; H, 4.98; N, 23.53; S, 13.38.

(Example 2) 3-amino-4-(diethylamino)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-33)

(2a) (2Z)-2-cyano-3-(diethylamino)but-2-enethioamide

(2Z)-2-cyano-3-ethoxybut-2-enethioamide (J.Org.Chem.,(1962),27,2433-2439) (406 mg, 2.38 mmol) and diethylamine (0.36 mL, 3.53 mmol) were suspended in ethanol (5 mL) and the mixture was stirred at room temperature for two hours. After the solvent was evaporated, the obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane =2:1) and the title compound was obtained (237 mg, yield 50%).

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.32 (6H, t, J = 7.04 Hz), 2.71 (3H, s), 3.65 (4H, q, J = 7.05 Hz), 6.69 (2H, br s).

(2b) 4-(diethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(diethylamino)but-2-enethioamide produced in Example 2 (2a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and reacted in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 54%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.19 (6H, t, J = 6.8 Hz), 3.21 (1H, s), 3.615 (4H, q, J = 6.8 Hz), 6.34 (1H, d, J = 7.8 Hz), 7.36 (1H, t, J = 7.8 Hz).

(2c) 3-amino-4-(diethylamino)thieno[2,3-b]pyridine-2-carboxamide

4-(diethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile produced in Example 2 (2b) was used in place of 4-(diethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and reacted in a similar method as described in Example 1 (1c) and the title compound was obtained. Yield 65%.

Mp 127-129°C;

IR (KBr) $\nu_{max}$ 3426, 3304, 3143, 2974, 1672, 1647, 1581, 1504, 1376, 1345, 1262, 1158, 1050, 790, 616 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 0.98 (6H, t, J = 7.0 Hz), 3.17 (4H, q, J = 7.0 Hz), 7.06 (1H, d, J = 5.1 Hz), 7.09 (2H, s), 7.36 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 264.10 $[M + H]^+$;

Anal. Calcd for $C_{12}H_{16}N_4OS$: C, 54.52; H, 6.10; N, 21.19; S, 12.13. Found: C, 54.18; H, 5.86; N, 21.34; S, 12.18.

(Example 3) 3-amino-4-(dimethylamino)-6-methylthieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-102)

(3a) 4-(dimethylamino) -6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile

2-chloro-4-(dimethylamino)-6-methylnicotinonitrile (Pharm.Chem.J.,(Engl. Transl.),25,(1991),623-628.) (1.46 g, 7.5 mmol) and thiourea (0.74 g, 9.7 mmol) were suspended in toluene (25 mL) and the mixture was stirred under reflux for four hours. Ethanol (40 mL) was added to the reaction mixture and further heated under reflux for 30 minutes. The solid which deposited after allowing to stand overnight at room temperature was filtered and washed with ethanol, water, ethanol sequentially and the title compound was obtained as a crude product (0.64 g).

$^1$H NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.20 (3H, s), 3.18 (6H, s), 6.23 (1H, s), 12.41 (1H, br).

(3b) 3-amino-4-(dimethylamino)-6-methylthieno[2,3-b]pyridine-2-carboxamide

4-(dimethylamino)-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (0.19 g, 1.0 mmol) produced in Example 3 (3a) was dissolved in N,N-dimethylformamide (3 mL) and 8N aqueous solution of sodium hydroxide (0.5 mL) and 2-chloroacetamide (0.11 g, 1.2 mmol) were added. After the mixture was stirred at room temperature for one hour, water (50 mL) was added. The aqueous layer was extracted with ethyl acetate (3x50 mL) and the extract was concentrated after drying over sodium sulfate under reduced pressure. The residue was purified by silica gel column chromatography (100% ethyl acetate) and 0.16 g of the title compound (yield 62%) was obtained.

Mp 167-170°C;

IR (KBr) $\nu_{max}$ 3442, 3327, 3170, 1647, 1580, 1368, 992 cm$^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 2.48 (3H, s), 2.78 (6H, s), 6.84 (1H, s), 6.93 (2H, br), 6.95 (2H, br);

MS (EI) m/z: 250 [$M^+$], 218, 205, 190;

Anal. Calcd for $C_{11}H_{14}N_4SO \cdot 0.5\ H_2O$: C, 50.95; H, 5.83; N, 21.60; S, 12.36. Found: C, 50.84; H, 5.94; N, 21.51; S, 12.19.

(Example 4) 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (Exemplified Compound No. 3-3)

(4a) (2Z)-2-cyano-3-(propylamino)but-2-enethioamide

(2Z)-2-cyano-3-ethoxybut-2-enethioamide (J.Org.Chem.,(1962),27,2433-2439) (0.34 g, 2.0 mmol) and propylamine (0.15 g, 2.5 mmol) were suspended in ethanol (5 mL) and the mixture was stirred at room temperature for 15 hours. The deposited solid was separated by filtration and further washed with ethanol and 0.29 g of the title compound (yield 79%) was obtained.

Mp 149-151°C;

IR (KBr) $\nu_{max}$ 3400, 3287, 3187, 2190, 1612 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 0.97 (3H, t, J = 7.4 Hz), 1.55-1.64 (2H, m), 2.30 (3H, s), 3.35-3.40 (2H, m), 7.65 (1H, br), 8.45 (1H, br), 12.74 (1H, br);

MS (FAB) m/z: 184 $[M+H]^+$;

Anal. Calcd for $C_8H_{13}N_3S$: C, 52.43; H, 7.15; N, 22.93; S, 17.49. Found: C, 52.59; H, 7.25; N, 22.83; S, 17.51.

(4b) 3-amino-4-(propylamino)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-(propylamino)but-2-enethioamide (0.29 g, 1.6 mmol) which was produced in Example 4 (4a) and N,N-dimethylformamide dimethylacetal (0.57 g, 4.7 mmol) were mixed with toluene (3 mL) and the mixture was stirred under heat reflux for two hours. 1N aqueous solution of sodium hydroxide (5 mL) was added to the residue which was obtained by evaporating the solvent under reduced pressure

and the mixture was stirred under heat reflux for 30 minutes. After the reaction mixture was cooled to room temperature, ether (20 mL) was added and the liquid was partitioned. Furthermore, the organic layer was extracted with 1N aqueous solution of sodium hydroxide (5 mL). The combined aqueous layer was neutralized with 1N hydrochloric acid, and the deposited solid was separated by filtration and further washed with water and a little amount of ethanol and a solid (0.17 g) mainly containing 2-thioxo-1,2-dihydropyridine derivative was obtained.

The obtained solid was dissolved in N,N-dimethylformamide (3 mL) and 8N aqueous solution of sodium hydroxide (0.5 mL) and 2-chloroacetamide (0.10 g, 1.1 mmol) were added. After the mixture was stirred at room temperature for one hour, water (3 mL) was added. The deposited solid was separated by filtration and washed with water and ethanol and 106 mg of the title compound was obtained.
Yield 27% from (2Z)-2-cyano-3-(propylamino)but-2-enethioamide.
Mp 214-215°C;
IR (KBr) $\nu_{max}$ 3348, 3319, 3189, 1650, 1592, 1504, 1364 $cm^{-1}$;
$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.95 (3H, t, J = 7.4 Hz), 1.59-1.68 (2H, m), 3.16-3.21 (2H, m), 6.41 (1H, d, J = 5.6 Hz), 6.44 (1H, brt, J = 5.4 Hz), 6.81 (2H, br), 7.02 (2H, br), 8.05 (1H, d, J = 5.6 Hz);
MS (EI) m/z: 250 [$M^+$], 204;
Anal. Calcd for $C_{11}H_{14}N_4OS \cdot 1.1H_2O$: C, 48.91; H, 6.04; N, 20.74; S, 11.87. Found: C, 49.06; H, 5.92; N, 20.71; S, 11.90.

(Example 5) 3-amino-4-(isobutylamino)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-6)
(5a) (2Z)-2-cyano-3-(isobutylamino)but-2-enethioamide

(2Z)-2-cyano-3-ethoxybut-2-enethioamide (J.Org.Chem.,(1962),27,2433-2439) (340 mg, 2.0 mmol) and isobutylamine (183 mg, 2.5 mmol) were suspended in

ethanol (3 mL) and the mixture was stirred at room temperature for six hours. After the deposited solid was separated by filtration, it was washed with ethanol and 378 mg of the title compound (96%) was obtained.

Mp 165-167°C;

IR (KBr) $\nu_{max}$ 3373, 3291, 3198, 2190, 1608 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.97 (6H, d, J = 6.7 Hz), 1.82-1.92 (1H, m), 2.30 (3H, s), 3.25-3.28 (2H, m), 7.67 (1H, br), 8.48 (1H, br), 12.76 (1H, br);

MS (FAB) m/z: 198 $[M+H]^+$;

Anal. Calcd for $C_9H_{15}N_3S$: C, 54.79; H, 7.66; N, 21.30; S, 16.25. Found: C, 54.73; H, 7.84; N, 21.24; S, 16.18.

(5b) 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(isobutylamino)but-2-enethioamide (360 mg, 1.8 mmol) which was produced in Example 5 (5a) and N,N-dimethylformamide dimethylacetal (652 mg, 5.5 mmol) were mixed with toluene (5 mL) and the mixture was stirred under reflux for two hours. 1N aqueous solution of sodium hydroxide (5 mL) was added to the residue which was obtained by evaporating the solvent under reduced pressure, and it was stirred under reflux for 30 minutes. After the reaction mixture was cooled to room temperature, the liquid was partitioned with ether (50 mL) and water (20 mL). The obtained aqueous layer was neutralized with 1N hydrochloric acid (5 mL) and the deposited solid was separated by filtration and further washed with water and a little amount of ethanol and 217 mg of a solid containing the title compound was obtained.

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.87 (6H, d, J = 6.7 Hz), 1.78-1.88 (1H, m), 3.06-3.12 (2H, m), 6.33 (1H, d, J = 7.4 Hz), 7.41 (1H, br), 7.50 (1H, br), 12.35 (1H, br).

(5c) 3-amino-4-(isobutylamino)thieno[2,3-b]pyridine-2-carboxamide

Crude product (215 mg, 1.0 mmol) of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 5 (5b) was dissolved

in N,N-dimethylformamide (3 mL) and 8N aqueous solution of sodium hydroxide (0.3 mL) and 2-chloroacetamide (126 mg, 1.3 mmol) were added. Water (3 mL) was added after the mixture was stirred at room temperature for one hour. The deposited solid was separated by filtration and washed with water and ethanol and 109 mg of the title compound was obtained. Yield 23% from 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile.

Mp 117-119°C;

IR (KBr) $\nu_{max}$ 3399, 3352, 3250, 3121, 1676, 1595, 860 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.95 (6H, d, J = 6.7 Hz), 1.90-2.01 (1H, m), 3.04-3.08 (2H, m), 6.43 (1H, d, J = 5.5 Hz), 6.52 (1H, br), 6.83 (2H, br), 7.08 (2H, br), 8.07 (1H, d, J = 5.5 Hz);

MS (EI) m/z: 264 [$M^+$], 204;

Anal. Calcd for $C_{12}H_{16}N_4OS \cdot 0.1H_2O$: C, 54.15; H, 6.14; N, 21.05; S, 12.05. Found: C, 54.11; H, 5.94; N, 21.06; S, 12.17.

(Example 6) 3-amino-4-(neopentylamino)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-7)

(6a) (2Z)-2-cyano-3-(neopentylamino)but-2-enethioamide

Neopentylamine was used in place of propylamine and the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 54%.

Mp 143-144°C;

IR (KBr) $\nu_{max}$ 3376, 3297, 3202, 2188, 1607 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.99 (9H, s), 2.30 (3H, s), 3.23 (2H, d, J = 5.5 Hz), 7.67 (1H, br), 8.49 (1H, br), 12.78 (1H, br);

MS (FAB) m/z: 212 $[M+H]^+$;

Anal. Calcd for $C_{10}H_{17}N_3S$: C, 56.84; H, 8.11; N, 19.88; S, 15.17. Found: C, 56.59; H, 8.09; N, 19.76; S, 14.90.

(6b) 3-amino-4-(neopentylamino)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-(neopentylamino)but-2-enethioamide which was produced in Example 6 (6a) was used in place of (2Z)-2-cyano-3-(propylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 4 (4b) and the title compound was obtained. Yield 16%.

Mp 238-240°C;

IR (KBr) $\nu_{max}$ 3318, 3190, 1653, 1587, 1105 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.97 (9H, s), 3.08 (2H, d, J = 6.1 Hz), 6.46 (1H, brt, J = 6.1 Hz), 6.54 (1H, d, J = 5.7 Hz), 6.63 (2H, br), 7.14 (2H, br), 8.06 (1H, d, J = 5.7 Hz);

MS (FAB) m/z: 279 $[M+H]^+$;

Anal. Calcd for $C_{13}H_{18}N_4OS \cdot 1.2H_2O$: C, 52.05; H, 6.85; N, 18.68; S, 10.69. Found: C, 52.31; H, 6.69; N, 18.68; S, 10.67.

(Example 7) 3-amino-4-(benzylamino)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-11)

(7a) (2Z)-3-(benzylamino) -2-cyanobut-2-enethioamide

Benzylamine was used in place of propylamine and the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 97%.

Mp 157-159°C;

IR (KBr) $\nu_{max}$ 3355, 3287, 3193, 2193, 1627, 1608, 853, 739 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.34 (3H, s), 4.69 (2H, d, J = 5.6 Hz), 7.31-7.43 (5H, m), 7.74 (1H, br), 8.55 (1H, br), 13.02 (1H, br);

MS (FAB) m/z: 232 $[M+H]^+$;

Anal. Calcd for $C_{12}H_{13}N_3S$: C, 62.31; H, 5.66; N, 18.17; S, 13.86. Found: C, 62.19; H, 5.88; N, 18.27; S, 13.66.

(7b) 4-(benzylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-3-(benzylamino) -2-cyanobut-2-enethioamide (0.41 g) which was produced in Example 7 (7a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product (0.38 g) of the title compound was obtained.

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 4.54 (2H, d, J = 6.3 Hz), 6.19 (1H, d, J = 7.4 Hz), 7.24-7.44 (5H, m), 8.12 (1H, br), 12.45 (1H, br).

(7c) 3-amino-4-(benzylamino)thieno[2,3-b]pyridine-2-carboxamide

A crude product (0.38 g) of 4-(benzylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 7 (7b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c), and 0.39 g of the title compound was obtained. Yield 73% from (2Z)-3-(benzylamino)-2-cyanobut-2-enethioamide.

Mp 260-262°C;

IR (KBr) $\nu_{max}$ 3460, 3394, 3351, 3112, 1654, 1627, 1598 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 4.52 (2H, d, J = 5.8 Hz), 6.28 (1H, d, J = 5.7 Hz), 6.95 (2H, br), 7.07 (2H, br), 7.16 (1H, brt, J = 5.8 Hz), 7.23-7.42 (5H, m), 8.00 (1H, d, J = 5.7 Hz);

MS (FAB) m/z: 299 $[M+H]^+$;

Anal. Calcd for $C_{15}H_{14}N_4OS$: C, 60.38; H, 4.73; N, 18.78; S, 10.75. Found: C, 60.37; H, 4.85; N, 18.87; S, 10.65.

(Example 8) 3-amino-4-[(2-phenethyl)amino]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-12)

(8a) (2Z)-2-cyano-3-[(2-phenethyl)amino]but-2-enethioamide

Phenethylamine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 75%.

Mp 95-96°C;

IR (KBr) $\nu_{max}$ 3353, 3300, 3203, 2189, 1626, 1595, 749, 699 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.22 (3H, s), 2.89 (2H, t, J = 7.2 Hz), 3.64-3.69 (1H, m), 7.18-7.31 (5H, m), 7.60 (1H, br), 8.40 (1H, br), 12.70 (1H, br);

MS (FAB) m/z: 246 $[M+H]^+$;

Anal. Calcd for $C_{13}H_{15}N_3S$: C, 63.64; H, 6.16; N, 17.13; S, 13.07. Found: C, 63.73; H, 6.11; N, 17.20; S, 13.14.

(8b) 3-amino-4-[(2-phenethyl)amino]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-[(2-phenethyl)amino]but-2-enethioamide (0.37 g, 1.5 mmol) which was produced in Example 8 (8a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and 0.34 g of a crude product of 2-thioxo-1,2-dihydropyridine derivative was obtained.

The reaction was performed in a similar method as described in Example 1 (1c) using the obtained 2-thioxo-1,2-dihydropyridine derivative and 0.25 g of the title compound was obtained (yield 53%).

Mp 206-208°C;

IR (KBr) $\nu_{max}$ 3449, 3358, 3121, 1656, 1598, 1514, 1103, 753, 703 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.93 (2H, t, J = 7.5 Hz), 3.44-3.49 (2H, m), 6.49 (1H, d, J = 5.7 Hz), 6.50 (1H, br), 6.76 (2H, br), 7.04 (2H, br), 7.18-7.32 (5H, m), 8.07 (1H, d, J = 5.7 Hz);

MS (FAB) m/z: 313 $[M+H]^+$;

Anal. Calcd for $C_{16}H_{16}N_4OS$: C, 61.52; H, 5.16; N, 17.93; S, 10.26. Found: C, 61.47; H, 5.25; N, 17.95; S, 10.33.

(Example 9) 3-amino-4-[(3-phenylpropyl)amino]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-13)

(9a) (2Z)-2-cyano-3-[(3-phenylpropyl)amino]but-2-enethioamide

3-phenyl propylamine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 94%.

Mp 125-126°C;

IR (KBr) $\nu_{max}$ 3399, 3285, 3173, 2189, 1612, 1603, 754, 531 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.85-1.92 (2H, m), 2.27 (3H, s), 2.70 (2H, t, J = 7.7 Hz), 3.37-3.42 (2H, m), 7.16-7.29 (5H, m), 7.64 (1H, br), 8.45 (1H, br), 12.79 (1H, br);

MS (FAB) m/z: 260 $[M+H]^+$;

Anal. Calcd for $C_{14}H_{17}N_3S$: C, 64.85; H, 6.61; N, 16.20; S, 12.36. Found: C, 65.02; H, 6.52; N, 16.28; S, 12.37.

(9b) 3-amino-4-[(3-phenylpropyl)amino]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-[(3-phenylpropyl)amino]but-2-enethioamide (0.49 g, 1.9 mmol) which was produced in Example 9 (9a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product of 2-thioxo-1,2-dihydropyridine derivative (0.45 g) was obtained.

The reaction was performed in a similar method as described in Example 1 (1c) using the obtained 2-thioxo-1,2-dihydropyridine derivative and 0.30 g of the title compound was obtained (yield 49%).

Mp 232-234°C;

IR (KBr) $\nu_{max}$ 3424, 3326, 3125, 1659, 1603, 1517, 1362 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.89-1.97 (2H, m), 2.69 (2H, t, J = 7.6 Hz), 3.21-3.26 (2H, m), 6.37 (1H, d, J = 5.6 Hz), 6.47 (1H, brt, J = 5.3 Hz), 6.81 (2H, br), 7.02 (2H, br), 7.15-7.29 (5H, m), 8.04 (1H, d, J = 5.6 Hz);

MS (FAB) m/z: 327 $[M+H]^+$;

Anal. Calcd for $C_{17}H_{18}N_4OS$: C, 62.55; H, 5.56; N, 17.16; S, 9.82. Found: C, 62.33; H, 5.76; N, 17.32; S, 9.68.

(Example 10) 3-amino-4-(cyclopentylamino)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-8)

(10a) (2Z)-2-cyano-3-(cyclopentylamino)but-2-enethioamide

Cyclopentylamine was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 89%.

Mp 162-163°C;

IR (KBr) $\nu_{max}$ 3368, 3287, 3196, 2192, 1612 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.53-1.74 (6H, m), 1.92-2.00 (2H, m), 2.33 (3H, s), 4.11-4.19 (1H, m), 7.63 (1H, br), 8.44 (1H, br), 12.94 (1H, brd, J = 7.5 Hz);

MS (FAB) m/z: 210 $[M+H]^+$;

Anal. Calcd for $C_{10}H_{15}N_3S$: C, 57.38; H, 7.22; N, 20.08; S, 15.32. Found: C, 57.39; H, 7.21; N, 19.98; S, 15.26.

(10b) 4-(cyclopentylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(cyclopentylamino)but-2-enethioamide (358 mg) which was produced in Example 10 (10a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar

method as described in Example 1 (1b) and a crude product (318 mg) of the title compound was obtained.

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.51-1.73 (6H, m), 1.90-1.98 (2H, m), 3.94-4.04 (1H, m), 6.37 (1H, d, J = 7.8 Hz), 7.44-7.49 (1H, m), 12.42 (1H, br).

(10c) 3-amino-4-(cyclopentylamino)thieno[2,3-b]pyridine-2-carboxamide

A crude product (318 mg) of 4-(cyclopentylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 10 (10b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, and the reaction was performed in a similar method as described in Example 1 (1c) and 261 mg of the title compound was obtained. Yield 55% from (2Z)-3-(cyclopentylamino)-2-cyanobut-2-enethioamide.

Mp 212-213°C;

IR (KBr) $\nu_{max}$ 3311, 3177, 1649, 1594, 1513, 1497 cm$^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.52-1.73 (6H, m), 2.01-2.08 (2H, m), 3.85-3.92 (1H, m), 6.21 (1H, brd, J = 6.4 Hz), 6.43 (1H, d, J = 5.6 Hz), 6.72 (2H, br), 7.07 (2H, br), 8.06 (1H, d, J = 5.6 Hz);

MS (EI) m/z: 276 [$M^+$], 231;

Anal. Calcd for $C_{13}H_{16}N_4OS$: C, 56.50; H, 5.84; N, 20.27; S, 11.60. Found: C, 56.31; H, 5.73; N, 20.13; S, 11.33.

(Example 11) 3-amino-4-(cyclohexylamino)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-9)

(11a) (2Z)-2-cyano-3-(cyclohexylamino)but-2-enethioamide

Cyclohexylamine was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 76%.

Mp 142-144°C;

IR (KBr) $\nu_{max}$ 3412, 3297, 3188, 2187, 1613, 1493, 1410 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.33-1.61 (6H, m), 1.81-1.93 (4H, m), 2.37 (3H, s), 3.55-3.64 (1H, m), 6.38 (1H, br), 6.69 (1H, br), 12.92 (1H, br);

MS (EI) m/z: 223 [$M^+$], 190.

(11b) 3-amino-4-(cyclohexylamino)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-(cyclohexylamino)but-2-enethioamide (0.33 g, 1.5 mmol) which was produced in Example 11 (11a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product (0.11 g) of 2-thioxo-1,2-dihydropyridine derivative was obtained.

The reaction was performed in a similar method as described in Example 1 (1c) using the obtained 2-thioxo-1,2-dihydropyridine derivative and 0.06 g of the title compound was obtained (yield 14%).

Mp 244-247°C;

IR (KBr) $\nu_{max}$ 3141, 1664, 1598, 1513, 1497, 1108 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.20-1.98 (10H, m), 3.43-3.50 (1H, m), 6.16 (1H, d, J = 7.5 Hz), 6.46 (1H, d, J = 5.7 Hz), 6.71 (2H, br), 7.08 (2H, br), 8.06 (1H, d, J = 5.7 Hz);

MS (FAB) m/z: 291 $[M+H]^+$;

Anal. Calcd for $C_{14}H_{18}N_4OS \cdot 0.3H_2O$: C, 56.85; H, 6.34; N, 18.94; S, 10.85. Found: C, 57.00; H, 6.27; N, 18.95; S, 10.61.

(Example 12) 3-amino-4-(cycloheptylamino)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 2-10)

(12a) (2Z)-2-cyano-3-(cycloheptylamino)but-2-enethioamide

Cycloheptylamine was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 74%.

Mp 132-134°C;

IR (KBr) $\nu_{max}$ 3380, 3295, 3200, 2189, 1609, 853 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.48-1.63 (10H, m), 1.85-1.92 (2H, m), 2.32 (3H, s), 3.90-3.97 (1H, m), 7.62 (1H, br), 8.43 (1H, br), 12.94 (1H, brd, J = 8.9 Hz);

MS (FAB) m/z: 238 $[M+H]^+$;

Anal. Calcd for $C_{12}H_{19}N_3S$: C, 60.72; H, 8.07; N, 17.70; S, 13.51. Found: C, 60.69; H, 8.12; N, 17.68; S, 13.41.

(12b) 4-(cycloheptylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(cycloheptylamino)but-2-enethioamide (339 mg) which was produced in Example 12 (12a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product (306 mg) of the title compound was obtained.

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.40-1.72 (10H, m), 1.76-1.85 (2H, m), 3.61-3.73 (1H, m), 6.30 (1H, d, J = 7.4 Hz), 6.82 (1H, br), 7.43 (1H, br), 12.35 (1H, br).

(12c) 3-amino-4-(cycloheptylamino)thieno[2,3-b]pyridine-2-carboxamide

A crude product (306 mg) of 4-(cycloheptylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 12 (12b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and 201 mg of the title compound was obtained. Yield 46% from (2Z)-2-cyano-3-(cycloheptylamino)but-2-enethioamide.

Mp 206-208°C;

IR (KBr) $\nu_{max}$ 3334, 1652, 1594, 1514, 1498, 1365 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.49-1.71 (10H, m), 1.93-1.98 (2H, m), 3.60-3.63 (1H, m), 6.21 (1H, d, J = 7.5 Hz), 6.35 (1H, d, J = 5.8 Hz), 6.70 (2H, br), 7.10 (2H, br), 8.08 (1H, d, J = 5.8 Hz);

MS (FAB) m/z: 305 $[M+H]^+$;

Anal. Calcd for $C_{15}H_{20}N_4OS \cdot 0.1H_2O$: C, 58.84; H, 6.65; N, 18.30; S, 10.47. Found: C, 58.77; H, 6.48; N, 18.22; S, 10.34.

(Example 13) 3-amino-4-pyrrolidin-1-ylthieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-15)

(13a) (2Z)-2-cyano-3-pyrrolidin-1-ylbut-2-enethioamide

Pyrrolidine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 86%

$^1H$ NMR($CD_3OD$, 400 MHz) δ 2.00 (4H, s), 2.47 (3H, s), 3.63 (4H, s).

(13b) 4-pyrrolidin-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-pyrrolidin-1-ylbut-2-enethioamide which was produced in Example 13 (13a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 80%.

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.91 (4H, s), 3.55-3.75 (4H, br s), 6.21 (1H, d, J = 7.3 Hz), 7.365 (1H, dd, J = 5.9, 7.3 Hz).

(13c) 3-amino-4-pyrrolidin-1-yl thieno[2,3-b]pyridine-2-carboxamide

4-pyrrolidin-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 13 (13b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 85%.

Mp 275-283°C;

IR (KBr) $\nu_{max}$ 3429, 3297, 3138, 2999, 2877, 1673, 1611, 1584, 1503, 1372, 1341, 1273, 1113, 1056, 1002, 618, 486 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.91 (4H, s), 3.30 (4H, s), 6.87 (1H, d, J = 5.8 Hz), 6.88 (2H, s), 7.02 (2H, br s), 8.255 (1H, d, J = 5.8 Hz);

MS (FAB) m/z: 262.08 $[M+H]^+$;

Anal. Calcd for $C_{12}H_{14}N_4OS$: C,54.94; H,5.38; N,21.36; S,12.22. Found: C,54.54; H,5.15; N,21.10; S,12.03.

(Example 14) 3-amino-4-piperidin-1-ylthieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-16)

(14a) (2Z)-2-cyano-3-piperidin-1-ylbut-2-enethioamide

An ethanol (30 mL) solution of (2Z)-2-cyano-3-ethoxybut-2-enethioamide (1.70 g, 10 mmol) and piperidine (1.02 g, 12 mmol) was stirred for two hours under heat reflux and allowed to stand overnight at room temperature. After the deposited solid was washed with ethanol (3x3 mL) and 1.36 g of the title compound was obtained (yield 65%).

Mp 161-166°C;

IR (KBr) $\nu_{max}$ 3381, 3268, 3170, 2182, 1600, 1534, 873, 838, 636 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.58-1.63 (6H, m), 2.27 (3H, s), 3.31-3.36 (4H, m), 8.15 (1H, br), 8.86 (1H, br);

MS (EI) m/z: 209 $[M^+]$, 150, 44;

Anal. Calcd for $C_{10}H_{15}N_3S$: C, 57.38; H, 7.22; N, 20.08; S, 15.32. Found: C, 57.27; H, 7.16; N, 20.03; S, 15.47.

(14b) 4-piperidin-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-piperidin-1-ylbut-2-enethioamide (0.42 g, 2.0 mmol) and N,N-dimethylformamide dimethylacetal (0.72 g, 6.0 mmol) which was produced in

Example 14 (14a) were mixed toluene (3 mL) and the mixture was stirred under reflux for two hours.

1N aqueous solution of sodium hydroxide (3 mL) was added to the residue which was obtained by evaporating the solvent under reduced pressure and the mixture was stirred under heat reflux for 30 minutes. After the reaction mixture was cooled to room temperature, 1N hydrochloric acid (4 mL) was added and the deposited solid was separated by filtration and further washed with water and a little amount of ethanol and 0.30 g of a solid containing the title compound was obtained.

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.50-1.55 (6H, m), 3.48-3.52 (4H, m), 6.38 (1H, d, J = 7.3 Hz), 7.35 (1H, d, J = 7.3 Hz).

(14c) 3-amino-4-piperidin-1-ylthieno[2,3-b]pyridine-2-carboxamide

4-piperidin-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (0.30 g) which was produced in Example 14 (14b) was dissolved in N,N-dimethylformamide (3 mL) and 8N aqueous solution of sodium hydroxide (0.6 mL) and 2-chloroacetamide (0.15 g, 1.6 mmol)were added. Water (5 mL) was added after the mixture was stirred at room temperature for one hour. The deposited solid was separated by filtration and washed with water and ethanol and 0.30 g of a solid was obtained. The obtained solid was purified by silica gel column chromatography (100% ethyl acetate) and 0.21 g of the title compound was obtained.

Yield 38% from (2Z)-2-cyano-3-piperidin-1-ylbut-2-enethioamide.

Mp 191-192°C;

IR (KBr) $\nu_{max}$ 3460, 3329, 3176, 1651, 1589, 1501, 1378, 963 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.72-1.79 (6H, m), 2.55-3.40 (4H, m), 6.93 (2H, br), 6.99 (1H, d, J = 5.1 Hz), 7.07 (2H, br), 8.40 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 277 $[M+H]^+$;

Anal. Calcd for $C_{13}H_{16}N_4SO \cdot 0.5\ H_2O$: C, 54.72; H, 6.00; N, 19.63; S, 11.24. Found: C, 54.68; H, 6.03; N, 19.67; S, 11.05.

(Example 15) 3-amino-4-(4-methylpiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-18)

(15a) (2Z)-2-cyano-3-(4-methylpiperidin-1-yl)but-2-enethioamide

4-methylpiperidine was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 87%.

Mp 156-159°C;

IR (KBr) $\nu_{max}$ 3387, 3262, 3162, 2177, 1604, 1540, 868 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.91 (3H, d, J = 6.1 Hz), 1.15-1.25 (2H, m), 1.62-1.73 (3H, m), 2.27 (3H, s), 3.04-3.10 (2H, m), 3.62 (2H, brd, J = 13.5 Hz), 8.14 (1H, br), 8.85 (1H, br);

MS (EI) m/z: 223 [$M^+$], 190;

Anal. Calcd for $C_{11}H_{17}N_3S \cdot 0.1\ H_2O$: C, 58.68; H, 7.70; N, 18.66; S, 14.27. Found: C, 58.92; H, 7.73; N, 18.77; S, 14.06.

(15b) 4-(4-methylpiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(4-methylpiperidin-1-yl)but-2-enethioamide (0.39 g) which was produced in Example 15 (15a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b). After the reaction terminated, toluene was added and the liquid was partitioned, and then the aqueous layer was neutralized with 1N hydrochloric acid and the deposited solid was separated by filtration and further washed with water and ethanol and a crude product (0.24 g) of the title compound was obtained.

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.93 (3H, d, J = 6.4 Hz), 1.14-1.24 (2H, m), 1.65-1.76 (3H, m), 3.10-3.16 (2H, m), 4.08 (2H, brd, J = 13.2 Hz), 6.49 (1H, d, J = 7.5 Hz), 7.44 (1H, d, J = 7.5 Hz), 12.60 (1H, br).

(15c) 3-amino-4-(4-methylpiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

A crude product (0.24 g) of 4-(4-methylpiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 15 (15b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, and the reaction was performed in a similar method as described in Example 5 (5c) and 0.24 g of the title compound was obtained. Yield 41% from (2Z)-2-cyano-3-(4-methylpiperidin-1-yl)but-2-enethioamide.

Mp 252-254°C;

IR (KBr) $\nu_{max}$ 3430, 3311, 3159, 1667, 1611, 1580, 1504, 1367, 1341 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.98 (3H, d, J = 6.0 Hz), 1.40-1.76 (5H, m), 2.66-2.80 (2H, m), 3.27-3.30 (2H, m), 6.91 (2H, br), 6.99 (1H, d, J = 5.2 Hz), 7.05 (2H, br), 8.39 (1H, d, J = 5.2 Hz);

MS (FAB) m/z: 291 $[M+H]^+$;

Anal. Calcd for $C_{14}H_{18}N_4SO$: C, 57.91; H, 6.25; N, 19.29; S, 11.04. Found: C, 57.89; H, 6.31; N, 19.29; S, 11.06.

(Example 16) 3-amino-4-(3-methylpiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-17)

(16a) 4-(3-methylpiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-ethoxybut-2-enethioamide (340 mg, 2.0 mmol) and 3-methylpiperidine (248 mg, 2.5 mmol) were mixed with ethanol (2 mL) and the mixture was stirred at room temperature for two hours. The residue which was obtained by concentrating the reaction mixture under reduced pressure was dissolved in toluene (6 mL) and was blended with N,N-dimethylformamide dimethylacetal (714 mg, 6.0 mmol) and the mixture was stirred under heat reflux for two hours. 1N aqueous solution of sodium hydroxide (4 mL) was added to the residue after the solvent was evaporated under reduced pressure. The mixture was stirred under heat

reflux for one hour and after it was cooled, 1N hydrochloric acid (5 mL) was added. After the deposited solid was washed with water and ethanol and 211 mg of a solid mainly containing the title compound was obtained.

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 0.89 (3H, d, J = 6.7 Hz), 1.14-1.25 (1H, m), 1.47-1.83 (4H, m), 2.82 (1H, dd, J = 10.6, 13.3 Hz), 3.08-3.15 (1H, m), 3.96-4.05 (2H, m), 6.50 (1H, d, J = 6.5 Hz), 7.42-7.45 (1H, m), 12.59 (1H, br).

(16b) 3-amino-4-(3-methylpiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

A solid (211 mg) mainly containing 4-(3-methylpiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 16 (16a) was dissolved in N,N-dimethylformamide (2 mL) and 8N aqueous solution of sodium hydroxide (0.2 mL) and 2-chloroacetamide (122 mg, 1.3 mmol) were added and the mixture was stirred at room temperature for one hour. Water (2 mL) was added to the reaction mixture and the deposited solid was separated by filtration and further washed with water and ethanol and 158 mg of the title compound was obtained.

Yield 27% from (2Z)-2-cyano-3-ethoxybut-2-enethioamide.

Mp 201-204°C;

IR (KBr) $\nu_{max}$ 3422, 3325, 3162, 1657, 1580, 1501, 1371 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 0.91 (3H, d, J = 6.3 Hz), 1.70-1.95 (4H, m), 2.23-2.70 (2H, m), 3.20-3.30 (2H, m), 6.90 (2H, br), 6.99 (1H, d, J = 5.1 Hz), 7.08 (2H, br), 8.40 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 291 $[M+H]^+$;

Anal. Calcd for $C_{14}H_{18}N_4SO \cdot 0.1\ H_2O$: C, 57.55; H, 6.28; N, 19.17; S, 10.97. Found: C, 57.45; H, 6.10; N, 19.35; S, 11.12.

(Example 17) 3-amino-4-[3-(hydroxymethyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-20)

(2Z)-2-cyano-3-ethoxybut-2-enethioamide (340 mg, 2.0 mmol) and 3-(hydroxymethyl)piperidine (288 mg, 2.5 mmol) were mixed with ethanol (3 mL) and the mixture was stirred at room temperature for 1.5 hours. The residue which was obtained by concentrating the reaction mixture under reduced pressure was dissolved in N,N-dimethylformamide (3 mL) and was blended with N,N-dimethylformamide dimethylacetal (250 mg, 2.1 mmol) and the mixture was stirred at room temperature for one hour and further at 100°C for one hour. The reaction mixture was cooled to room temperature and was blended with 8N aqueous solution of sodium hydroxide (0.4 mL) and 2-chloroacetamide (281 mg, 3.0 mmol) and the mixture was stirred at room temperature for one hour. Water (50 mL) and ethyl acetate (50 mL) were added to the reaction mixture and the liquid was partitioned, and further the aqueous layer was extracted with ethyl acetate (30 mL). Combined with the organic layer, the solvent was evaporated under reduced pressure after drying over sodium sulfate. The residue was purified by silica gel column chromatography (dichloromethane/methanol =10:1) and 146 mg of the title compound was obtained. Yield 24% from (2Z)-2-cyano-3-ethoxybut-2-enethioamide.

Mp 125-130°C;

IR (KBr) $\nu_{max}$ 3441, 3335, 3183, 1661, 1595, 1583, 1503, 1375, 1037 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.95-1.15 (1H, m), 1.70-1.99 (4H, m), 2.26-2.70 (2H, m), 3.21-3.43 (4H, m), 4.56 (1H, t, J = 5.3 Hz), 6.94 (2H, br), 7.02 (1H, d, J = 5.1 Hz), 7.11 (2H, br), 8.44 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 307 $[M+H]^+$;

Anal. Calcd for $C_{14}H_{18}N_4SO_2 \cdot 1\ H_2O$: C, 51.84; H, 6.21; N, 17.27; S, 9.88. Found: C, 51.72; H, 6.15; N, 17.37; S, 9.70.

(Example 18) 3-amino-4-(4-benzylpiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-19)

(18a) (2Z)-3-(4-benzylpiperidin-1-yl) -2-cyanobut-2-enethioamide

4-benzylpiperidine was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 88%.

Mp 151-154°C;

IR (KBr) $\nu_{max}$ 3283, 3173, 2187, 1605, 1542, 867, 749, 702 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.26-1.32 (2H, m), 1.63-1.66 (2H, m), 1.80-1.90 (1H, m), 2.53 (2H, d, J = 7.2 Hz), 3.02-3.08 (2H, m), 3.65 (2H, brd, J = 13.6 Hz), 7.17-7.31 (1H, m), 8.18 (1H, br), 8.88 (1H, br);

MS (EI) m/z: 299 [$M^+$], 240, 91;

Anal. Calcd for $C_{17}H_{21}N_3S \cdot 0.3\ H_2O$: C, 66.98; H, 7.14; N, 13.78; S, 10.52. Found: C, 67.03; H, 6.97; N, 13.78; S, 10.36.

(18b) 4-(4-benzylpiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(4-benzylpiperidin-1-yl)but-2-enethioamide (0.53 g) which was produced in Example 18 (18a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b). The aqueous layer was neutralized with 1N hydrochloric acid after was added toluene after the reaction terminated, the liquid was partitioned, and the deposited solid was separated by filtration and further washed with water and ethanol and a crude product (0.23 g) of the title compound was obtained.

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.20-1.31 (2H, m), 1.69 (2H, brd, J = 10.9 Hz), 1.82-1.88 (1H, m), 2.54 (2H, d, J = 7.1 Hz), 3.05-3.11 (2H, m), 4.07 (2H, brd, J = 13.2 Hz), 6.45 (1H, d, J = 7.5 Hz), 7.40-7.44 (1H, m), 12.57 (1H, br).

(18c) 3-amino-4-(4-benzylpiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

A crude product (0.53 g) of 4-(4-benzylpiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 18 (18b) was used in

place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained (0.20 g).

Yield 27% from (2Z)-2-cyano-3-(4-benzylpiperidin-1-yl)but-2-enethioamide.

Mp 220-221°C;

IR (KBr) $\nu_{max}$ 3446, 3330, 3156, 1649, 1579, 1502, 1367, 958, 748, 700 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.48-1.72 (5H, m), 2.52-2.73 (2H, m), 2.59 (2H, d, J = 6.4 Hz), 3.30-3.33 (2H, m), 6.94 (2H, br), 6.99 (1H, d, J = 5.3 Hz), 7.09 (2H, br), 7.18-7.32 (5H, m), 8.41 (1H, d, J = 5.3 Hz);

MS (FAB) m/z: 367 $[M+H]^+$;

Anal. Calcd for $C_{20}H_{22}N_4SO \cdot 0.1\ H_2O$: C, 65.23; H, 6.08; N, 15.21; S, 8.71. Found: C, 65.18; H, 6.15; N, 15.35; S, 8.54.

(Example 19) 3-amino-4-(4-hydroxypiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-32)

(19a) (2Z)-2-cyano-3-(4-hydroxypiperidin-1-yl)but-2-enethioamide

4-hydroxypiperidine was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 93%.

Mp 160-163°C;

IR (KBr) $\nu_{max}$ 3368, 3167, 2180, 1634, 1536, 1415 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.44-1.52 (2H, m), 1.78-1.83 (2H, m), 2.27 (3H, s), 3.15-3.22 (2H, m), 3.50-3.56 (2H, m), 3.75-3.79 (1H, m), 4.82 (1H, d, J = 3.8 Hz), 8.18 (1H, br), 8.88 (1H, br);

MS (FAB) m/z: 226 $[M+H]^+$;

Anal. Calcd for $C_{10}H_{15}N_3SO$: C, 53.31; H, 6.71; N, 18.65; S, 14.23. Found: C, 53.14; H, 6.65; N, 18.54; S, 14.03.

(19b) (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-(4-hydroxypiperidin-1-yl)but-2-enethioamide

(2Z)-2-cyano-3-(4-hydroxypiperidin-1-yl)but-2-enethioamide (0.22 g, 1.0 mmol) and N,N-dimethylformamide dimethylacetal (0.13 g, 1.1 mmol) which was produced in Example 19 (19a) were mixed with ethanol (3 mL) and the mixture was stirred at room temperature for three hours. The deposited solid was separated by filtration and further washed with ethanol and 0.27 g of the title compound was obtained (yield 96%).

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.49-1.57 (2H, m), 1.83-1.90 (2H, m), 2.50 (3H, s), 2.99 (3H, s), 3.15 (3H, s), 3.32-3.39 (2H, m), 3.63-3.69 (2H, m), 3.80-3.86 (1H, m), 4.88 (1H, d, J = 3.9 Hz), 8.50 (1H, s);

(19c) 3-amino-4-(4-hydroxypiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-(4-hydroxypiperidin-1-yl)but-2-enethioamide (0.27 g) which was produced in Example 19 (19b) was dissolved in N,N-dimethylformamide (5 mL) and the mixture was stirred at 120°C for one hour. The reaction liquid was cooled to room temperature and 8N aqueous solution of sodium hydroxide (0.3 mL) and 2-chloroacetamide (0.11 g, 1.2 mmol) were added. Water (5 mL) was added after the mixture was stirred at room temperature for one hour. The deposited solid was separated by filtration and washed with water and ethanol and 0.05 g of the title compound was obtained (yield 18%).

Mp 239-241°C;

IR (KBr) $\nu_{max}$ 3445, 3425, 3330, 1645, 1592, 1376, 1045 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.63-1.71 (2H, m), 1.90-1.98 (2H, m), 2.70-3.30 (4H, m), 3.50-3.80 (1H, m), 4.77 (1H, br), 6.91 (2H, br), 7.00 (1H, d, J = 5.3 Hz), 7.06 (2H, br), 8.39 (1H, d, J = 5.3 Hz);

MS (FAB) m/z: 293 $[M+H]^+$;

Anal. Calcd for $C_{13}H_{16}N_4SO_2 \cdot 0.1\ H_2O$: C, 53.08; H, 5.55; N, 19.05; S, 10.90. Found: C, 53.09; H, 5.37; N, 18.77; S, 10.99.

(Example 20) 3-amino-4-(4-acetoxypiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-34)

3-amino-4-(4-hydroxypiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (0.10 g, 0.3 mmol) which was produced in Example 19 (19c) and acetic acid anhydride (0.2 mL) was reacted overnight in tetrahydrofuran (5 mL) solvent at room temperature in the presence of a catalytic amount of N,N-dimethylaminopyridine. A saturated sodium bicarbonate aqueous solution (30 mL) was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (50 mL). The extract was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The obtained solid was washed with ethyl acetate and 0.04 g of the title compound was obtained (yield 35%).

Mp 231-235°C;

IR (KBr) $\nu_{max}$ 3439, 3422, 3323, 1710, 1645, 1580, 1268, 1035, 963 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.82-2.10 (4H, m), 2.04 (3H, s), 2.70-3.45 (4H, m), 4.65-5.00 (1H, m), 6.91 (2H, br), 7.02 (1H, d, J = 5.3 Hz), 7.09 (2H, br), 8.41 (1H, d, J = 5.3 Hz);

MS (FAB) m/z: 335 $[M+H]^+$;

Anal. Calcd for $C_{15}H_{18}N_4SO_3 \cdot 0.24\ H_2O$: C, 53.19; H, 5.50; N, 16.54; S, 9.47. Found: C, 53.47; H, 5.27; N, 16.20; S, 9.22.

(Example 21) 3-amino-4-(4-phenyl-3,6-dihydropyridin-1(2H)-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-38)

(21a) (2Z)-2-cyano-3-(4-phenyl-3,6-dihydropyridin-1(2H)-yl)but-2-enethioamide

4-phenyl-1,2,3,6-tetrahydropyridine was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 99%.

Mp 170-171°C;

IR (KBr) $\nu_{max}$ 3342, 3293, 3189, 2176, 1637, 1555, 1410, 872, 750 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.36 (3H, s), 2.64-2.71 (2H, m), 3.64 (2H, t, J = 5.5 Hz), 3.98-4.04 (2H, m), 6.16 (1H, brs), 7.24-7.45 (5H, m), 8.33 (1H, br), 9.02 (1H, br);

MS (FAB) m/z: 284 $[M+H]^+$;

Anal. Calcd for $C_{16}H_{17}N_3S \cdot 0.2\ H_2O$: C, 66.96; H, 6.11; N, 14.64; S, 11.17. Found: C, 67.02; H, 6.12; N, 14.62; S, 10.81.

(21b) 4-phenyl-2'-thioxo-1',2',3,6-tetrahydro-2H-1,4'-bipyridine-3'-carbonitrile

(2Z)-2-cyano-3-(4-phenyl-3,6-dihydropyridine-1(2H)-yl)but-2-enethioamide (1.13 g) which was produced in Example 21 (21a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product (0.13 g) of the title compound was obtained.

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.66-2.72 (2H, m), 3.88-3.91 (2H, m), 4.26-4.30 (2H, m), 6.24 (1H, brs), 6.56 (1H, d, J = 7.8 Hz), 7.27-7.53 (6H, m), 12.70 (1H, br).

(21c) 3-amino-4-(4-phenyl-3,6-dihydropyridin-1(2H)-yl)thieno[2,3-b]pyridine-2-carboxamide

A crude product (0.13 g) of 4-phenyl-2'-thioxo-1',2',3,6-tetrahydro-2H-1,4'-bipyridine-3'-carbonitrile which was produced in Example 21 (21b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound (0.06 g) was obtained. Yield 4% from (2Z)-2-cyano-3-(4-phenyl-3,6-dihydropyridine-1(2H)-yl)but-2-enethioamide

Mp 235°C (decomposition);

IR (KBr) $\nu_{max}$ 3435, 3325, 1646, 1583, 1369, 954, 747 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.62-2.76 (2H, m), 3.30-3.46 (2H, m), 3.77-3.86 (2H, m), 6.35 (1H, brs), 6.90 (2H, br), 7.09 (1H, d, J = 5.3 Hz), 7.10 (2H, br), 7.25-7.51 (5H, m), 8.43 (1H, d, J = 5.3 Hz);

MS (FAB) m/z: 351 $[M+H]^+$;

Anal. Calcd for $C_{19}H_{18}N_4SO \cdot 0.7\ H_2O$: C, 62.86; H, 5.39; N, 15.43; S, 8.87. Found: C, 63.16; H, 5.04; N, 15.23; S, 8.45.

(Example 22)

3-amino-4-morpholin-4-ylthieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-41)

(22a) (2Z)-2-cyano-3-morpholin-1-ylbut-2-enethioamide

Morpholine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 85%.

Mp 156-160°C;

IR (KBr) $\nu_{max}$ 3374, 3255, 3165, 2177, 1605, 1540, 1119, 985, 884 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.26 (3H, s), 3.36-3.39 (4H, m), 3.64-3.67 (4H, m), 8.38 (1H, br), 9.06 (1H, br);

MS (FAB) m/z: 212 $[M+H]^+$;

Anal. Calcd for $C_9H_{13}N_3SO$: C, 51.16; H, 6.20; N, 19.89; S, 15.18. Found: C, 51.15; H, 6.14; N, 19.73; S, 15.17.

(22b) 4-morpholin-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile

4-(dimethoxymethyl) morpholine (Nucleosides and Nucleotides, 12, 1033-1046, (1993)) was used in place of N,N-dimethylformamide dimethylacetal and (2Z)-2-cyano-3-morpholin-1-ylbut-2-enethioamide was used in place of (2Z)-2-

cyano-3-piperidin-1-ylbut-2-enethioamide and the reaction was performed in a similar method as described in Example 14 (14b). The aqueous solution iobtained by removing insolubles by filtration from the reaction mixture was neutralized with 1N hydrochloric acid. The deposited solid was separated by filtration and washed with water and ethanol and a crude product of the title compound was obtained. Yield 43%.

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 3.62-3.65 (4H, m), 3.69-3.71 (4H, m), 6.51 (1H, d, J = 7.8 Hz), 7.52 (1H, d, J = 7.8 Hz) 12.75 (1H, br).

(22c) 3-amino-4-morpholin-4-ylthieno[2,3-b]pyridine-2-carboxamide

4-morpholin-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 22 (22b) was used in place of 4-piperidin-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile, the reaction was performed in a similar method as described in Example 14 (14c) and the title compound was obtained. Yield 64%.

Mp 232-234°C;

IR (KBr) $\nu_{max}$ 3427, 3377, 3170, 1670, 1579, 1501, 1373, 1112, 969 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 2.90-3.15 (4H, m), 3.84-3.86 (4H, m), 6.95 (2H, br), 7.05 (1H, d, J = 5.3 Hz), 7.13 (2H, br), 8.46 (1H, d, J = 5.3 Hz);

MS (FAB) m/z: 279 $[M+H]^+$;

Anal. Calcd for $C_{12}H_{14}N_4SO_2 \cdot 0.3\ H_2O$: C, 50.80; H, 5.19; N, 19.75; S, 11.30. Found: C, 50.95; H, 4.86; N, 19.72; S, 11.28.

(Example 23) 3-amino-4-(2,6-cis-dimethylmorpholin-4-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-42)

(2Z)-2-cyano-3-ethoxybut-2-enethioamide (340 mg, 2.0 mmol) and 2,6-cis-dimethylmorpholine (288 mg, 2.5 mmol) were mixed with ethanol (3 mL) and the mixture was stirred at room temperature for four hours. The obtained residue by evaporating the solvent under reduced pressure was dissolved in N,N-

dimethylformamide (3 mL) and N,N-dimethylformamide dimethylacetal (262 mg, 2.2 mmol) was added. The reaction mixture was stirred at 100°C for one hour after stirring at room temperature for one hour. After cooled to room temperature, 8N aqueous solution of sodium hydroxide (0.4 mL) and 2-chloroacetamide (243 mg, 2.6 mmol) were added to the reaction mixture. The reaction mixture was partitioned with water (50 mL) and ethyl acetate (50 mL) after stirring at room temperature for one hour. The solvent was evaporated under reduced pressure after the organic layer was dried over sodium sulfate. Residue silica was purified by gel column chromatography (ethyl acetate/ethanol/triethylamine =30:1:1) and 100 mg of the title compound was obtained (16%).

Mp 242-244°C;

IR (KBr) $\nu_{max}$ 3441, 3326, 3172, 1650, 1584, 1502, 1373, 1082, 1010 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.13 (6H, d, J = 6.3 Hz), 2.40-2.50 (2H, m), 3.24 (2H, brd, J = 11.3 Hz), 3.90-3.98 (2H, m), 6.92 (2H, br), 7.03 (1H, d, J = 5.1 Hz), 7.16 (2H, br), 8.45 (1H, d, J = 5.1 Hz);

MS (EI) m/z: 306 [$M^+$], 202;

Anal. Calcd for $C_{14}H_{18}N_4SO_2$: C, 54.88; H, 5.92; N, 18.29; S, 10.47. Found: C, 54.88; H, 5.99; N, 18.37; S, 10.43.

(Example 24) 3-amino-4-thiomorpholin-4-ylthieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-44)

(24a) (2Z)-2-cyano-3-thiomorpholin-4-ylbut-2-enethioamide

Thiomorpholine was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 73%.

Mp 157-160°C (decomposition);

IR (KBr) $\nu_{max}$ 3346, 3285, 3180, 2183, 1534, 953, 865 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 2.26 (3H, s), 2.72-2.74 (4H, m), 3.58-3.61 (4H, m), 8.43 (1H, br), 9.11 (1H, br);

MS (FAB) m/z: 228 $[M+H]^+$;

Anal. Calcd for $C_9H_{13}N_3S_2 \cdot 0.1\ H_2O$: C, 47.17; H, 5.81; N, 18.34; S, 27.98. Found: C, 47.27; H, 5.82; N, 18.62; S, 27.84.

(24b) 4-thiomorpholin-4-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-thiomorpholin-4-ylbut-2-enethioamide (250 mg) which was produced in Example 24 (24a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product (157 mg) of the title compound was obtained.

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 2.74-2.77 (4H, m), 3.84-3.87 (4H, m), 6.49 (1H, d, J = 7.4 Hz), 7.48 (1H, brd, J = 7.4 Hz), 12.73 (1H, br).

(24c) 3-amino-4-thiomorpholin-4-ylthieno[2,3-b]pyridine-2-carboxamide

A crude product (157 mg) of 4-thiomorpholin-4-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 24 (24b) was dissolved in N,N-dimethylformamide (2 mL) and 8N aqueous solution of sodium hydroxide (0.2 mL) and 2-chloroacetamide (74 mg, 0.8 mmol) were added. Water (2 mL) was added to the reaction mixture after stirring at room temperature one hour. The deposited solid was separated by filtration and washed with water and ethanol. The obtained crystal was further heated and the mixture was stirred in ethyl acetate. After cooling, crystal was separated by filtration and 37 mg of the title compound was obtained. Yield 11% from (2Z)-2-cyano-3-thiomorpholin-4-ylbut-2-enethioamide.

Mp 255-258°C;

IR (KBr) $\nu_{max}$ 3439, 3322, 3166, 1656, 1582, 1502, 1374, 1344, 935 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 2.50-3.60 (8H, m), 6.93 (2H, br), 7.04 (1H, d, J = 5.3 Hz), 7.10 (2H, br), 8.43 (1H, d, J = 5.3 Hz);

MS (EI) m/z: 294 [$M^+$], 202;

Anal. Calcd for $C_{12}H_{14}N_4S_2O$: C, 48.96; H, 4.79; N, 19.03; S, 21.78. Found: C, 48.90; H, 4.70; N, 19.04; S, 21.73.

(Example 25) 3-amino-4-azepan-1-ylthieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-39)

(25a) (2Z)-3-azepan-1-yl-2-cyanobut-2-enethioamide

Hexamethyleneimine was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 94%.

Mp 158-161°C;

IR (KBr) $\nu_{max}$ 3405, 3292, 3184, 2192, 1607, 1517, 1009, 870 $cm^{-1}$;

$^1$H NMR ($CDCl_3$, 400MHz) δ 1.61-1.70 (4H, m), 1.87-1.95 (4H, m), 2.74 (3H, s), 3.70-3.73 (4H, m), 6.69 (2H, br);

MS (EI) m/z: 223 [$M^+$], 190;

Anal. Calcd for $C_{11}H_{17}N_3S$: C, 59.16; H, 7.67; N, 18.81; S, 14.36. Found: C, 59.10; H, 7.72; N, 18.67; S, 14.07.

(25b) 4-azepan-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-3-azepan-1-yl-2-cyanobut-2-enethioamide (0.42 g) which was produced in Example 25 (25a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product (0.38 g) of the title compound was obtained.

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.49-1.54 (4H, m), 1.73-1.80 (4H, m), 3.75-3.78 (4H, m), 6.39 (1H, d, J = 7.8 Hz), 7.37 (1H, dd, J = 6.0, 7.8 Hz), 12.46 (1H, br).

(25c) 3-amino-4-azepan-1-ylthieno[2,3-b]pyridine-2-carboxamide

A crude product (0.38 g) of 4-azepan-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 25 (25b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, the reaction was performed in a similar method as described in Example 5 (5c) and 0.39 g of the title compound was obtained. Yield 71% from (2Z)-3-azepan-1-yl-2-cyanobut-2-enethioamide.

Mp 219-221°C;

IR (KBr) $\nu_{max}$ 3436, 3298, 3131, 1673, 1582, 1371, 930 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.65-1.78 (8H, m), 3.25-3.28 (4H, m), 7.04 (4H, br), 7.05 (1H, d, J = 5.4 Hz), 8.38 (1H, d, J = 5.4 Hz);

MS (EI) m/z: 290 [$M^+$], 202.

(Example 26) 3-amino-4-azocan-1-ylthieno[2,3-b]pyridine-2-carboxamide

(Exemplified Compound No. 1-40)

(26a) (2Z)-3-azocan-1-yl-2-cyanobut-2-enethioamide

Heptamethyleneimine was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 85%.

Mp 149-150°C;

IR (KBr) $\nu_{max}$ 3340, 3276, 3164, 2176, 1631, 1558, 848 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.45-1.52 (6H, m), 1.72-1.75 (4H, m), 2.34 (3H, s), 3.55-3.58 (4H, m), 8.30 (1H, br), 8.92 (1H, br);

MS (FAB) m/z: 238 $[M+H]^+$;

Anal. Calcd for $C_{12}H_{19}N_3S \cdot 0.06\ H_2O$: C, 60.45; H, 8.08; N, 17.62; S, 13.45. Found: C, 60.43; H, 7.93; N, 17.67; S, 13.58.

(26b) 4-azocan-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-3-azocan-1-yl-2-cyanobut-2-enethioamide (0.39 g) which was produced in Example 26 (26a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product (0.35 g) of the title compound was obtained.
$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.44-1.57 (6H, m), 1.71-1.74 (4H, m), 3.80-3.83 (4H, m), 6.38 (1H, d, J = 7.7 Hz), 7.35-8.38 (1H, m), 12.48 (1H, br).

(26c) 3-amino-4-azocan-1-ylthieno[2,3-b]pyridine-2-carboxamide

A crude product (0.35 g) of 4-azocan-1-yl-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 26 (26b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, and the reaction was performed in a similar method as described in Example 5 (5c) and 0.36 g of the title compound was obtained.
Yield 72% from (2Z)-3-azocan-1-yl-2-cyanobut-2-enethioamide.
Mp 222-224°C;
IR (KBr) $\nu_{max}$ 3440, 3300, 3132, 1667, 1579, 1499, 1372, 990 cm$^{-1}$;
$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.60-1.75 (10H, m), 3.34-3.36 (4H, m), 7.03 (2H, br), 7.04 (2H, br), 7.08 (1H, d, J = 5.4 Hz), 8.35 (1H, d, J = 5.4 Hz);
MS (FAB) m/z: 305 $[M+H]^+$;
Anal. Calcd for $C_{15}H_{20}N_4SO$: C, 58.84; H, 6.65; N, 18.30; S, 10.47. Found: C, 58.84; H, 6.53; N, 18.30; S, 10.37.

(Example 27) 3-amino-4-(3,4-dihydroisoquinoline-2(1H)-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-35)

(27a) (2Z) 2-cyano-3-(3,4-dihydroisoquinoline-2(1H)-yl)but-2-enethioamide

1,2,3,4-tetras hydro-isoquinoline was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 93%.

IR (KBr) $\nu_{max}$ 3284, 3167, 2186, 1609, 1538, 878, 752 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.38 (3H, s), 2.95 (2H, t, J = 5.8 Hz), 3.62 (2H, t, J = 5.8 Hz), 4.54 (2H, s), 7.10-7.21 (4H, m), 8.32 (1H, br) 8.98 (1H, br);

MS (EI) m/z: 257 [$M^+$], 224.

(27b) 4-(3,4-dihydroisoquinoline-2(1H)-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(3,4-dihydroisoquinoline-2(1H)-yl)but-2-enethioamide (470 mg) which was produced in Example 27 (27a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product (175 mg) of the title compound was obtained.

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 3.00 (2H, t, J = 5.9 Hz), 3.88 (2H, t, J = 5.9 Hz), 4.76 (2H, s), 6.58 (1H, d, J = 7.4 Hz), 7.22-7.25 (4H, m), 7.51-7.54 (1H, m) 12.72 (1H, br).

(27c) 3-amino-4-(3,4-dihydroisoquinoline-2(1H)-yl)thieno[2,3-b]pyridine-2-carboxamide

A crude product (175 mg) of 4-(3,4-dihydroisoquinoline-2(1H)-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 27 (27b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained (71 mg). Yield 12% from (2Z)-2-cyano-3-(3,4-dihydroisoquinoline-2(1H)-yl)but-2-enethioamide.

Mp 244-245°C;

IR (KBr) $\nu_{max}$ 3395, 3325, 3144, 1659, 1585, 1502, 1378, 739 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.94-3.10 (2H, m), 3.33-3.50 (2H, m), 4.28 (2H, brs), 6.85 (2H, br), 7.08 (1H, d, J = 5.5 Hz), 7.09 (2H, br), 7.17-7.19 (4H, m), 8.44 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 325 $[M+H]^+$;

Anal. Calcd for $C_{17}H_{16}N_4SO$: C, 62.94; H, 4.97; N, 17.27; S, 9.88. Found: C, 62.69; H, 5.24; N, 17.21; S, 9.85.

(Example 28) 3-amino-4-(trans-perhydroisoquinolin-2-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-36)

(28a) (2Z)-2-cyano-3-(trans-perhydroisoquinolin-2-yl)but-2-enethioamide

Trans-perhydroisoquinoline was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 41%.

Mp 142-147°C;

IR (KBr) $\nu_{max}$ 3375, 3277, 3163, 2184, 1606, 1537, 872 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.88-1.72 (12H, m), 2.27 (3H, s), 2.71-2.77 (1H, m), 3.04-3.11 (1H, m), 3.49-3.51 (1H, m), 3.64-3.68 (1H, m), 8.15 (1H, br), 8.87 (1H, br);

MS (FAB) m/z: 264 $[M+H]^+$;

Anal. Calcd for $C_{14}H_{21}N_3S$: C, 63.84; H, 8.04; N, 15.95; S, 12.17. Found: C, 63.92; H, 7.98; N, 15.93; S, 11.91.

(28b) 4-(trans-perhydroisoquinolin-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(trans-perhydroisoquinolin-2-yl)but-2-enethioamide (210 mg) which was produced in Example 28 (28a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product (153 mg) of the title compound was obtained.

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.91-1.74 (12H, m), 2.75-2.81 (1H, m), 3.09-3.15 (1H, m), 3.94-4.00 (1H, m), 4.10-4.17 (1H, m), 6.48 (1H, d, J = 7.4 Hz), 7.39-7.43 (1H, m), 12.56 (1H, br).

(28c) 3-amino-4-(trans-perhydroisoquinolin-2-yl)[2,3-thieno b]pyridine-2-carboxamide

A crude product (153 mg) of 4-(trans-perhydroisoquinolin-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 28 (28b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained (115 mg).

Yield 44% from (2Z)-2-cyano-3-(trans-perhydroisoquinolin-2-yl)but-2-enethioamide.

Mp 285-288°C;

IR (KBr) $\nu_{max}$ 3406, 3323, 3143, 1656, 1584, 1502, 1377, 951 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 0.92-1.76 (12H, m), 2.34-2.45 (1H, m), 2.66-2.79 (1H, m), 3.14-3.22 (1H, m), 3.30-3.38 (1H, m), 6.92 (2H, br), 7.01 (1H, d, J = 5.1 Hz), 7.10 (2H, br), 8.42 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 331 $[M+H]^+$;

Anal. Calcd for $C_{17}H_{22}N_4SO$: C, 61.79; H, 6.71; N, 16.95; S, 9.70. Found: C, 61.63; H, 6.71; N, 16.94; S, 9.74.

(Example 29) 3-amino-4-(cis-perhydroisoquinolin-2-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-36)

(29a) (2Z)-2-cyano-3-(cis-perhydroisoquinolin-2-yl)but-2-enethioamide

cis-perhydroisoquinoline was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 95%.

Mp 173-175°C;

IR (KBr) $\nu_{max}$ 3444, 3250, 3160, 2188, 1603, 1542, 867 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.23-1.95 (12H, m), 2.27 (3H, s), 3.12-3.25 (2H, m), 3.41-3.54 (2H, m), 8.12 (1H, br), 8.85 (1H, br);

MS (FAB) m/z: 264 $[M+H]^+$;

Anal. Calcd for $C_{14}H_{21}N_3S$: C, 63.84; H, 8.04; N, 15.95; S, 12.17. Found: C, 63.53; H, 8.10; N, 15.67; S, 12.32.

(29b) 4-(cis-perhydroisoquinolin-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(cis-perhydroisoquinolin-2-yl)but-2-enethioamide (490 mg) which was produced in Example 29 (29a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and a crude product (370 mg) of the title compound was obtained.

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.22-1.95 (12H, m), 3.10-3.43 (2H, m), 3.78-3.94 (2H, m), 6.47 (1H, d, J = 7.4 Hz), 7.40 (1H, d, J = 7.4 Hz), 12.40 (1H, br).

(29c) 3-amino-4-(cis-perhydroisoquinolin-2-yl)thieno[2,3-b]pyridine-2-carboxamide

A crude product (370 mg) of 4-(cis-perhydroisoquinolin-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 29 (29b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained (200 mg). Yield 33% from (2Z)-2-cyano-3-(cis-perhydroisoquinolin-2-yl)but-2-enethioamide.

Mp 224-226°C;

IR (KBr) $\nu_{max}$ 3443, 3323, 3179, 1646, 1582, 1503, 1370, 957 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.20-2.25 (12H, m), 2.92-3.46 (4H, m), 6.93 (2H, br), 7.03 (1H, d, J = 5.1 Hz), 7.08 (2H, br), 8.40 (1H, d, J = 5.1 Hz);

MS (EI) m/z: 330 $[M^+]$, 285;

Anal. Calcd for $C_{17}H_{22}N_4SO \cdot 0.1H_2O$: C, 61.46; H, 6.73; N, 16.86; S, 9.65. Found: C, 61.37; H, 6.76; N, 16.80; S, 9.68.

(Example 30) 3-amino-4-(1,4-oxazepan-4-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-43)

(30a) (2Z)-2-cyano-3-(1,4-oxazepan-4-yl)but-2-enethioamide

Homomorpholine was used in place of isobutylamine, the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 151-156°C;

IR (KBr) $\nu_{max}$ 3348, 3285, 3174, 2184, 1632, 1518, 1417, 1127, 1075, 878, 814 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.86-1.92 (2H, m), 2.31 (3H, s), 3.57 (2H, t, J = 5.5 Hz), 3.62 (2H, t, J = 5.5 Hz), 3.66 (2H, t, J = 5.5 Hz), 3.77 (2H, t, J = 5.5 Hz), 8.29 (1H, brs), 8.94 (1H, brs);

HRMS m/z calcd for $C_{10}H_{16}ON_3S$ 226.1014, found 226.1019;

MS (FAB) m/z: 226 $[M+H]^+$, 209, 192, 165, 65, 51.

(30b) 4-(1,4-oxazepan-4-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(1,4-oxazepan-4-yl)but-2-enethioamide which was produced in Example 30 (30a) was used in place of (2Z)-2-cyano-3-(isobutylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 5 (5b) and the title compound was obtained.

White powder

Mp 228-233°C (decomposition);

IR (KBr) $\nu_{max}$ 3119, 2952, 2210, 1625, 1520, 1252, 1117, 928, 780 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.89-1.94 (2H, m), 3.67 (2H, t, J = 5.5 Hz), 3.77-3.79 (2H, m), 3.33-3.37 (4H, m), 6.44 (1H, d, J = 7.8 Hz), 7.42 (1H, d, J = 7.8 Hz), 12.59 (1H, brs);

HRMS m/z calcd for $C_{11}H_{13}ON_3S$ 235.0779, found 235.0790;

MS (EI) m/z: 235 $[M^+]$, 204, 190, 177, 164, 150, 136, 108, 76, 70, 41.

(30c) 3-amino-4-(1,4-oxazepan-4-yl)thieno[2,3-b]pyridine-2-carboxamide

4-(1,4-oxazepan-4-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 30 (30b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

White powder

Mp 175-176°C;

IR (KBr) $\nu_{max}$ 3445, 3301, 3141, 1671, 1585, 1497, 1370, 1153, 1060, 940 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.99-2.05 (2H, m), 3.30-3.34 (4H, m), 3.78-3.84 (4H, m), 7.05 (2H, brs), 7.08-7.10 (3H, m), 8.41 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{13}H_{17}O_2N_4S$ 293.1073, found 293.1067;

MS (FAB) m/z: 293 $[M+H]^+$, 276, 237, 183, 165, 120, 65;

Anal. Calcd for $C_{13}H_{16}N_4O_2S \cdot 0.28H_2O$: C, 52.50; H, 5.61; N, 18.84; S, 10.78. Found: C, 52.32; H, 5.41; N, 19.03, S, 10.77.

(Example 31) 3-amino-4-(4-phenylpiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-26)

(31a) (2Z)-2-cyano-3-(4-phenylpiperidin-1-yl)but-2-enethioamide

4-phenylpiperidine was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 171-172°C;

IR (KBr) $\nu_{max}$ 3389, 3263, 3162, 2185, 1599, 1535, 1364, 1232, 980, 855, 764, 701 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.69-1.86 (4H, m), 2.33 (3H, s), 2.83-2.91 (1H, m), 3.22 (2H, t, J = 12.1 Hz), 3.76 (2H, d, J = 12.1 Hz), 7.19-7.83 (5H, m), 8.28 (1H, brs), 8.98 (1H, brs);

HRMS m/z calcd for $C_{16}H_{20}N_3S$ 286.1378, found 286.1372;

MS (FAB) m/z: 286 $[M+H]^+$, 252, 227, 186, 80, 56, 41;

Anal. Calcd for $C_{16}H_{19}N_3S$: C, 67.33; H, 6.71; N, 14.72; S, 11.23. Found: C, 67.10; H, 6.75; N, 14.65, S, 11.17.

(31b) (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-(4-phenylpiperidin-1-yl)but-2-enethioamide

(2Z)-2-cyano-3-(4-phenylpiperidin-1-yl)but-2-enethioamide (373 mg, 1.3 mmol) which was produced in Example 31 (31a) and N,N-dimethylformamide dimethylacetal (312 mg, 2.6 mmol) were mixed with ethanol (12 mL) and the mixture was stirred for 18 hours. The deposited solid was separated by filtration and 446 mg of the title compound was obtained (yield 70%).

Yellow powder

Mp 151-152°C;

IR (KBr) $\nu_{max}$ 2920, 2182, 1614, 1520, 1333, 1289, 1191, 975, 767, 704 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.79-1.91 (4H, m), 2.55 (3H, s), 2.94-3.00 (1H, m), 3.02 (3H, s) 3.18 (3H, s), 3.30-3.36 (2H, m), 3.93 (2H, d, J = 13.7 Hz), 7.20-7.83 (5H, m), 8.55 (1H, s);

HRMS m/z calcd for $C_{19}H_{25}N_4S$ 341.1800, found 341.1797;

MS (FAB) m/z: 341 $[M+H]^+$, 273, 246, 200, 165, 63;

Anal. Calcd for $C_{19}H_{24}N_4S \cdot 0.26H_2O$: C, 66.11; H, 7.16; N, 16.23; S, 9.29. Found: C, 66.15; H, 6.97; N, 16.14, S, 8.99.

(31c) 3-amino-4-(4-phenylpiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

N,N-dimethylformamide (1.8 mL) solution of (2Z)-2-cyano-N-[(1E)-(dimethylamino) methylene]-3-(4-phenylpiperidin-1-yl)but-2-enethioamide (299 mg,

N of 0.88 mmol) which was produced in Example 31 (31b) was stirred at 80°C for 15 minutes. 8N aqueous solution of sodium hydroxide (0.37 mL) and 2-chloroacetamide (99 mg, 1.1 mmol) were added after the reaction mixture was cooled to room temperature. Water and ethyl acetate was added after the mixture was stirred at room temperature for one hour. The deposited solid was separated by filtration and 310 mg of the title compound was obtained (yield 58%).

Pale yellow crystal

Mp 226-233°C;

IR (KBr) $\nu_{max}$ 3445, 3315, 3130, 1647, 1580, 1501, 1371, 1229, 1052, 959, 701 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.90 (2H, d, J = 11.7 Hz), 2.03 (2H, q, J = 11.7 Hz), 2.70 (1H, t, J = 11.7 Hz), 2.82-2.91 (2H, m), 3.45 (2H, d, J = 11.7 Hz), 7.02 (2H, brs), 7.07 (1H, d, J = 5.4 Hz), 7.10 (2H, brs), 7.22 (1H, t, J = 7.3 Hz), 7.33 (2H, t, J = 7.3 Hz), 7.38 (2H, d, J = 7.3 Hz), 8.46 (1H, d, J = 5.4 Hz);

HRMS m/z calcd for $C_{19}H_{20}ON_4S$ 352.1358, found 352.1358;

MS (FAB) m/z: 353 $[M+H]^+$, 273, 246, 200, 165, 63.

(Example 32) 3-amino-4-(1-oxothiomorpholine-4-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-45)

3-amino-4-(thiomorpholine-4-yl)thieno[2,3-b]pyridine-2-carboxamide (73 mg, 0.25 mmol) which was produced in Example 24 (24c) was dissolved in methanol and an aqueous solution (1 mL) of sodium periodate (59 mg, 0.28 mmol) was added. A saturated saline solution was added to the reaction liquid after stirring at room temperature for one hour and the aqueous layer was extracted with a mixed solvent of chloromethane/2-propanol (4:1). The extract was concentrated after drying over sodium sulfate under reduced pressure.

The residue was washed with ether and 78 mg of the title compound was obtained (yield 92%).

Pale yellow powder

Mp 165-172°C;

IR (KBr) $\nu_{max}$ 3431, 3323, 3183, 1649, 1589, 1500, 1375, 1057, 933 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.95-3.04 (2H, m), 3.21-3.32 (4H, m), 3.52-3.57 (2H, m), 6.99 (2H, brs), 7.15 (3H, brs), 8.48 (1H, d, J = 5.4 Hz);

HRMS m/z calcd for $C_{12}H_{14}O_2N_4S_2$ 310.0558, found 310.0555;

MS (EI) m/z: 310 [$M^+$], 278, 261, 244, 230, 202, 189, 176, 148, 122, 101, 76.

(Example 33) 3-amino-4-(1,4-thiazepan-4-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-46)

(33a) (2Z)-2-cyano-3-(1,4-thiazepan-4-yl)but-2-enethioamide

Homothiomorpholine (J. Org. Chem., 25, 1953-1956 (1960)) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

White powder

Mp 138-142°C;

IR (KBr) $\nu_{max}$ 3438, 23284, 3173, 1597, 1533, 1409, 1251, 867, 569 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.95-2.01 (2H, m), 2.33 (3H, s), 2.67 (2H, t, J = 5.9 Hz), 2.94 (2H, t, J = 5.5 Hz), 3.65 (2H, t, J = 5.9 Hz), 3.70 (2H, t, J = 5.5 Hz), 8.46 (1H, brs), 9.07 (1H, brs);

HRMS m/z calcd for $C_{10}H_{15}N_3S_2$ 241.0707, found 241.0707;

MS (EI) m/z: 241 [$M^+$], 208, 182, 142, 135, 121, 96, 68, 59, 43;

Anal. Calcd for $C_{10}H_{15}N_3S_2$: C, 49.76; H, 6.26; N, 17.41; S, 26.57. Found: C, 49.47; H, 6.32; N, 17.14, S, 26.48.

(33b) 4-(1,4-thiazepan-4-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(1,4-thiazepan-4-yl)but-2-enethioamide which was produced in Example 33 (33a) was used in place of (2Z)-2-cyano-3-(isobutylamino)but-2-

enethioamide and the reaction was performed in a similar method as described in Example 5 (5b) and the title compound was obtained.

Yellow powder

Mp 265-270°C;

IR (KBr) $\nu_{max}$ 3115, 2949, 2207, 1625, 1524, 1256, 1136, 943, 788 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.96 (2H, quint, J = 5.5 Hz), 2.62 (2H, t, J = 5.9 Hz), 2.90 (2H, t, J = 5.9 Hz), 3.97 (2H, t, J = 5.9 Hz), 4.04 (2H, t, J = 5.9 Hz), 6.42 (1H, d, J = 7.8 Hz), 7.37 (1H, d, J = 7.8 Hz), 12.48 (1H, brs);

HRMS m/z calcd for $C_{11}H_{13}N_3S_2$ 251.0551, found 251.0553;

MS (EI) m/z: 251 [$M^+$], 236, 223, 204, 190, 177, 164, 150, 136, 108, 60;

Anal. Calcd for $C_{11}H_{13}N_3S_2$: C, 52.56; H, 5.21; N, 16.72; S, 25.51. Found: C, 52.41; H, 5.37; N, 17.01, S, 25.62.

(33c) 3-amino-4-(1,4-thiazepan-4-yl)thieno[2,3-b]pyridine-2-carboxamide

4-(1,4-thiazepan-4-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 33 (33b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Pale yellow powder

Mp 171-174°C;

IR (KBr) $\nu_{max}$ 3416, 3302, 3171, 1645, 1582, 1498, 1367, 1259, 1125, 481 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.94-1.99 (2H, m), 2.76 (2H, t, J = 5.9 Hz), 2.98 (2H, t, J = 5.9 Hz), 3.29-3.32 (2H, m), 3.44-3.46 (2H, m), 7.07 (2H, brs), 7.20 (1H, d, J = 5.4 Hz), 7.41 (2H, brs), 8.46 (1H, d, J = 5.4 Hz);

HRMS m/z calcd for $C_{13}H_{16}ON_4S_2$ 308.0765, found 308.0767;

MS (EI) m/z: 308 [$M^+$], 276, 244, 230, 202, 188, 176, 148, 122, 78, 45;

Anal. Calcd for $C_{13}H_{16}N_4OS_2 \cdot 0.66H_2O$: C, 48.75; H, 5.45; N, 17.49. Found: C, 48.44; H, 5.38; N, 17.79.

(Example 34) 3-amino-4-(1-oxo-1,4-thiazepan-4-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-47)

3-amino-4-(1,4-thiazepan-4-yl)thieno[2,3-b]pyridine-2-carboxamide which was produced in Example 33 (33c) was used in place of 3-amino-4-(thiomorpholine-4-yl)thieno[2,3-b]pyridine-2-carboxamide and the reaction was performed in a similar method as described in Example 32 and the title compound was obtained.

Pale yellow powder

Mp 111-119°C;

IR (KBr) $\nu_{max}$ 3432, 3321, 1648, 1590, 1499, 1368, 1035 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 2.03-2.11 (1H, m), 2.59-2.67 (1H, m), 2.98-3.11 (2H, m), 3.19-3.30 (2H, m), 3.36-3.54 (3H, m), 3.91-3.96 (1H, m), 5.30 (2H, brs), 7.00 (1H, d, J = 4.9 Hz), 7.15 (2H, brs), 8.53 (1H, d, J = 4.9 Hz);

HRMS m/z calcd for $C_{13}H_{17}O_2N_4S_2$ 325.0793, found 325.0774;

MS (FAB) m/z: 325 $[M+H]^+$, 273, 178, 165, 51;

(Example 35) 3-amino-4-(3-phenylpiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-25)

(35a) (2Z)-2-cyano-3-(3-phenylpiperidin-1-yl)but-2-enethioamide

3-phenylpiperidine was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale brown powder

Mp 159-162°C (decomposition);

IR (KBr) $\nu_{max}$ 3307, 3184, 2190, 1600, 1533, 1412, 1260, 978, 850, 703 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.65-1.94 (4H, m), 2.32 (3H, s), 2.85-2.91 (1H, m), 3.12-3.19 (2H, m), 3.63 (1H, d, J = 11.2 Hz), 3.74 (1H, d, J = 11.2 Hz), 7.22-7.33 (5H, m), 8.30 (1H, brs), 8.99 (1H, brs);

HRMS m/z calcd for $C_{16}H_{19}N_3S$ 285.1299, found 285.1286;

MS (EI) m/z: 285 [$M^+$], 251, 226, 186, 160, 135, 109, 104, 91, 59;

Anal. Calcd for $C_{16}H_{19}N_3S$: C, 67.33; H, 6.71; N, 14.72; S, 11.23. Found: C, 67.25; H, 6.81; N, 14.53, S, 11.04.

(35b) 4-(3-phenylpiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(3-phenylpiperidin-1-yl)but-2-enethioamide which was produced in Example 35 (35a) was used in place of (2Z)-2-cyano-3-(isobutylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 5 (5b) and the title compound was obtained.

Pale brown powder

Mp 236-238°C (decomposition);

IR (KBr) $\nu_{max}$ 3118, 2939, 2208, 1622, 1515, 1449, 1309, 1251, 1164, 974, 758, 700 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.64-1.98 (4H, m), 2.84-2.90 (1H, m), 3.18-3.22 (2H, m), 4.12-4.15 (2H, m), 6.55 (1H, d, J = 7.3 Hz), 7.22-7.86 (5H, m), 7.46 (1H, d, J = 7.3 Hz), 12.66 (1H, brs);

HRMS m/z calcd for $C_{17}H_{18}N_3S$ 296.1222, found 296.1196;

MS (FAB) m/z: 296 [M+H]$^+$, 273, 242, 165, 65, 51;

(35c) 3-amino-4-(3-phenylpiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

4-(3-phenylpiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 35 (35b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Pale yellow powder

Mp 267-269°C;

IR (KBr) $\nu_{max}$ 3444, 3328, 3173, 2932, 1643, 1578, 1500, 1370, 1247, 1053, 966, 700 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.58-1.73 (1H, m), 1.86-2.02 (3H, m), 2.73-2.80 (2H, m), 3.09-3.16 (1H, m), 3.38-3.41 (2H, m), 6.99 (2H, brs), 7.06 (1H, d, J = 5.1 Hz), 7.12 (2H, brs), 7.20-7.33 (5H, m), 8.43 (1H, d, J = 5.1 Hz);

HRMS m/z calcd for $C_{19}H_{20}ON_4S$ 352.1358, found 352.1360;

MS (EI) m/z: 352 [$M^+$], 334, 307, 274, 252, 233, 202, 176, 91, 77, 73;

Anal. Calcd for $C_{19}H_{20}N_4OS \cdot 0.34H_2O$: C, 63.64; H, 5.81; N, 15.62; S, 8.94. Found: C, 63.32; H, 5.57; N, 15.87, S, 8.69.

(Example 36) 3-amino-4-(3-hydroxypiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-27)

(36a) (2Z)-2-cyano-3-(3-hydroxypiperidin-1-yl)but-2-enethioamide

3-hydroxypiperidine was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 159-162°C (decomposition);

IR (KBr) $\nu_{max}$ 3287, 2939, 2184, 1601, 1539, 1407, 1261, 1071, 859 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.42-1.52 (2H, m), 1.74-1.86 (2H, m), 2.27 (3H, s), 3.03 (1H, dd, J = 7.8, 13.3 Hz), 3.11-3.16 (1H, m), 3.44 (1H, dd, J = 3.4, 13.3 Hz), 3.59-3.64 (1H, m), 5.01 (1H, d, J = 4.7 Hz), 8.14 (1H, brs), 8.91 (1H, brs);

HRMS m/z calcd for $C_{10}H_{16}ON_3S$ 226.1014, found 226.1024;

MS (FAB) m/z: 226 [$M+H]^+$, 192, 171, 65;

Anal. Calcd for $C_{10}H_{15}N_3OS \cdot 0.04H_2O$: C, 53.14; H, 6.72; N, 18.59; S, 14.19. Found: C, 53.00; H, 6.52; N, 18.47, S, 14.15.

(36b) 4-(3-hydroxypiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(3-hydroxypiperidin-1-yl)but-2-enethioamide which was produced in Example 36 (36a) was used in place of (2Z)-2-cyano-3-(isobutylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 5 (5b) and the title compound was obtained.

Brown powder

Mp 202-206°C;

IR (KBr) $\nu_{max}$ 3119, 2945, 2208, 1625, 1522, 1251, 1173, 995, 962, 773 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.46-1.53 (2H, m), 1.79-1.88 (2H, m), 3.29 (1H, dd, J = 7.8, 13.2 Hz), 3.39-3.44 (1H, m), 3.60-3.71 (2H, m), 3.80 (1H, dd, J = 3.4, 13.2 Hz), 6.48 (1H, d, J = 7.8 Hz), 7.44 (1H, d, J = 7.8 Hz), 12.59 (1H, brs).

(36c) 3-amino-4-(3-hydroxypiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

4-(3-hydroxypiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 36 (36b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Yellow powder

Mp 208-211°C;

IR (KBr) $\nu_{max}$ 3325, 1633, 1594, 1501, 1374, 1243, 959 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.60-2.02 (4H, m), 3.16-3.96 (5H, m), 6.38 (2H, brs), 6.99 (1H, d, J = 5.1 Hz), 7.05 (2H, brs), 8.40 (1H, d, J = 5.1 Hz);

HRMS m/z calcd for $C_{13}H_{16}O_2N_4S$ 292.0994, found 292.1013;

MS (EI) m/z: 292 [$M^+$], 274, 256, 252, 218, 201, 176, 148, 128, 122, 43;

Anal. Calcd for $C_{13}H_{16}N_4O_2S \cdot 0.16H_2O$: C, 52.89; H, 5.57; N, 18.98; S, 10.86. Found: C, 53.11; H, 5.55; N, 18.61, S, 10.86.

(Example 37) tert-butyl 4-[3-amino-2-(aminocarbonyl)thieno[2,3-b]pyridin-4-yl]piperazine-1-carboxylate (Exemplified Compound No. 3-75)

(37a) tert-butyl 4-[(1Z)-3-amino-2-cyano-1-methyl-3-thioxoprop-1-enyl]piperazine-1-carboxylate

tert-butyl piperazine-1-carboxylate was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 40%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.41 (9H, s), 2.27 (3H, s), 3.36-3.46 (8H, m), 8.36 (1H, s), 9.06 (1H, s).

(37b) tert-butyl 4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperazine-1-carboxylate

tert-butyl 4-[(1Z)-3-amino-2-cyano-1-methyl-3-thioxoprop-1-enyl]piperazine-1-carboxylate which was produced in Example 37 (37a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 69%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.49 (9H, s), 3.44-3.49 (4H, m), 3.61-3.66 (4H, m), 6.45 (1H, d, J = 7.4 Hz), 6.49 (1H, d, J = 7.4 Hz).

(37c) tert-butyl 4-[3-amino-2-(aminocarbonyl)thieno[2,3-b]pyridin-4-yl]piperazine-1-carboxylate

tert-butyl 4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperazine-1-carboxylate which was produced in Example 37 (37b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 90%.

Mp 198-203°C;

IR (KBr) $\nu_{max}$ 3428, 3323, 3176, 2974, 1693, 1649, 1584, 1501, 1367, 1241, 1169, 1124, 976, 959, 825, 770 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.42 (9H, s), 3.25(4H, s), 3.29 (4H, s), 6.95 (2H, br s), 7.03 (1H, d, J = 5.4 Hz), 7.12 (2H, br s), 8.45 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 378 $[M+H]^+$;

Anal. Calcd for $C_{17}H_{23}N_5O_3S \cdot 0.3H_2O$: C,53.33; H,6.21; N,18.29; S,8.37. Found: C,53.14; H,5.86; N,18.06; S,8.41.

(Example 38) 3-amino-4-piperazin-1-ylthieno[2,3-b]pyridine-2-carboxamide dihydrochloride (Exemplified Compound No. 3-1)

tert-butyl 4-[3-amino-2-(aminocarbonyl)thieno[2,3-b]pyridin-4-yl]piperazine-1-carboxylate (326 mg, 0.86 mmol) which was produced in Example 37 (37c) was suspended in 1,4-dioxane (10 mL) and was blended with 4N hydrochloric acid-dioxane (4 mL) and the mixture was stirred for two hours. After the solvent was evaporated, obtained yellow solid was dried under vacuum, and the title compound was obtained (316 mg, yield 100%).

Mp 270-280°C;

IR (KBr) $\nu_{max}$ 3320, 3180, 2925, 2770, 2717, 1648, 1604, 1446, 1395, 1259, 1059, 973, 906, 797, 556, 540, 516 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 3.58-4.28 (8H, br s), 7.125 (1H, d, J = 5.1 Hz), 7.24 (2H, br s), 8.525 (1H, d, J = 5.1 Hz), 9.45 (2H, br s);

MS (FAB) m/z: 278 $[M+H]^+$;

Anal. Calcd for $C_{12}H_{15}N_5OS \cdot 2HCl \cdot H_2O$: C,39.14; H,5.20; N,19.02. Found: C,38.99; H,5.13; N,18.77.

(Example 39) 3-amino-4-(4-methylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-2)

(39a) (2Z)-2-cyano-3-(4-methylpiperazin-1-yl)but-2-enethioamide

1-methylpiperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 85%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.18 (3H, s), 2.26 (3H, s), 2.38 (4H, m), 3.35 (4H, m), 8.29 (1H, br s), 8.99 (1H, br s).

(39b) 3-amino-4-(4-methylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-(4-methylpiperazin-1-yl)but-2-enethioamide which was produced in Example 39 (39a) (301 mg, 1.34 mmol) and dimethylformamide dimethylacetal (0.53 mL, 4.01 mmol) were suspended in toluene (5 mL) and the mixture was stirred under reflux for three minutes. After cooling to room temperature, 1N aqueous solution of sodium hydroxide (3.50 mL) was added to the obtained residue by evaporating the solvent and it was heated for 30 minutes under reflux. After cooling to room temperature, 4N hydrochloric acid -dioxane solution (5 mL) was added and the pH value of solution was adjusted to around 3. The mixture was concentrated under reduced pressure and 2-chloroacetamide (126 mg, 1.35 mmol), 8N aqueous solution of sodium hydroxide (2.5 mL), dimethylformamide (5 mL) were added to the obtained residue and the mixture was stirred for three hours. Water (10 mL) was added to the reaction mixture and allowed to stand still for one week. The solid which resulted was filtered and the title compound was obtained (99 mg, yield 26%).

Mp 260-263°C;

IR (KBr) $\nu_{max}$ 3502, 3424, 3322, 3161, 2939, 2801, 1653, 1588, 1502, 1451, 1371, 1344, 1288, 1246, 1199, 973, 819, 737, 683, 625, 476 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.26 (3H, s), 2.40-2.72 (4H, br s), 2.85-3.22 (4H, br s), 6.89 (2H, br s), 7.00 (1H, d, J = 5.5 Hz), 7.07 (2H, s), 8.41 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 291 $[M+H]^+$;

Anal. Calcd for $C_{13}H_{17}N_5OS \cdot 0.3H_2O$: C,52.61; H,5.98; N,23.60; S,10.80. Found: C,52.62; H,5.79; N,23.63; S,10.92.

(Example 40) 3-amino-4-(4-ethyl piperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-3)

(40a) (2Z)-2-cyano-3-(4-ethyl piperazin-1-yl)but-2-enethioamide

1-ethyl piperazine was used in place of propylamine and the title compound was obtained and the reaction was performed in a similar method as described in Example 4 (4a). Yield 67%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.00 (3H, t, J = 7.0 Hz), 2.25 (3H, s), 2.36 (2H, q, J = 7.0 Hz), 2.49 (4H, m), 3.36 (4H, m), 8.29 (1H, br s), 8.99 (1H, br s).

(40b) 3-amino-4-(4-ethyl piperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-(4-ethyl piperazin-1-yl)but-2-enethioamide (299 mg, 1.25 mmol) which was produced in Example 40 (40a) and dimethylformamide dimethylacetal (0.50 mL, 3.77 mmol) were suspended in toluene (5 mL) and the mixture was stirred under reflux for three minutes. After the reaction mixture was cooled to room temperature, 1N aqueous solution of sodium hydroxide (3.50 mL) was added to the obtained residue by evaporating the solvent, and heated under reflux for 40 minutes. After cooling to room temperature, 4N hydrochloric acid - dioxane solution (2 mL) was added and the pH value of solution was adjusted to around 4. The mixture was concentrated under reduced pressure and 2-chloroacetamide (118 mg, 1.27 mmol), 8N aqueous solution of sodium hydroxide (2.5 mL), dimethylformamide (5 mL) were added to the obtained residue and it was stirred for three hours. Water (10 mL) was added to the reaction mixture and the solid which resulted after allowing to stand still for one day was filtered and the title compound was obtained (123 mg, yield 32%).

Mp 218-219°C;

IR (KBr) $\nu_{max}$ 3425, 3316, 3173, 2968, 2821, 1644, 1581, 1503, 1448, 1375, 1346, 1243, 1136, 975, 826, 770, 735, 542, 478 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.04 (3H, t, J = 7.0 Hz), 2.415 (2H, q, J = 7.0 Hz), 2.46-3.24 (8H, br s), 6.89 (2H, s), 7.015 (1H, d, J = 5.5 Hz), 7.08 (2H, s), 8.415 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 306 $[M+H]^+$;

Anal. Calcd for $C_{14}H_{19}N_5OS \cdot 0.5H_2O$: C,53.48; H,6.41; N,22.27; S,10.20. Found: C,53.54; H,6.05; N,22.17; S,10.27.

(Example 41) 3-amino-4-(4-isopropyl piperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-5)

(41a) (2Z)-2-cyano-3-(4-isopropyl piperazin-1-yl)but-2-enethioamide

1-isopropyl piperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 67%.

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 0.955 (6H, d, J = 6.7 Hz), 2.25 (3H, s), 2.36 (2H, q, J = 7.0 Hz), 2.48 (4H, m), 2.65 (1H, m), 3.34 (4H, m), 8.25 (1H, br s), 8.94 (1H, br s).

(41b) 3-amino-4-(4-isopropyl piperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-(4-isopropyl piperazin-1-yl)but-2-enethioamide (299 mg, 1.18 mmol) which was produced in Example 41 (41a) and dimethylformamide dimethylacetal (0.47 mL, 3.56 mmol) were suspended in toluene (5 mL) and the mixture was stirred under reflux for three minutes. After the reaction mixture was cooled to room temperature, 1N aqueous solution of sodium hydroxide (3.50 mL) was added to the obtained residue by evaporating the solvent, and heated under reflux for 40 minutes. After cooling to room temperature, 1N hydrochloric acid (5 mL) was added and the pH value of solution was adjusted to around 4. The solid which resulted was removed by filtration and the obtained filtrate was concentrated

under reduced pressure. 2-chloroacetamide (153 mg, 1.64 mmol), 8N aqueous solution of sodium hydroxide (5 mL), dimethylformamide (1.5 mL) were added to the residue and the mixture was stirred for three hours. Water (10 mL) was added to the reaction mixture and the solid which resulted was filtered and washed with diisopropyl ether (4x3 mL) and the title compound was obtained (137 mg, yield 28%).

Mp 240-243°C;

IR (KBr) $\nu_{max}$ 3413, 3322, 3121, 2964, 2827, 1660, 1584, 1502, 1448, 1376, 1345, 1245, 1176, 1134, 982, 820, 766, 741, 646, 486 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.015 (6H, d, J = 6.3 Hz), 2.40-3.40 (9H, br s), 6.90 (2H, br s), 7.00 (1H, d, J = 5.5 Hz), 7.06 (2H, s), 8.40 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 319 $[M+H]^+$;

Anal. Calcd for $C_{15}H_{21}N_5OS \cdot 0.19H_2O$: C,55.80; H,6.67; N,21.69; S,9.93. Found: C,55.82; H,6.53; N,21.63; S,10.06.

(Example 42) 3-amino-4-(4-phenylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-9)

(42a) (2Z)-2-cyano-3-(4-phenylpiperazin-1-yl)but-2-enethioamide

1-phenylpiperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 60%.

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.31 (3H, s), 3.27 (4H, m), 3.51 (4H, m), 6.78 (1H, t, J = 7.1 Hz), 6.92 (2H, d, J = 7.8 Hz), 7.21 (2H, m), 8.36 (1H, s), 9.05 (1H, s).

(42b) 4-(4-phenylpiperazin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(4-phenylpiperazin-1-yl)but-2-enethioamide which was produced in Example 42 (42a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar

method as described in Example 1 (1b) and the title compound was obtained. Yield 77%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 3.31 (4H, m), 3.80 (4H, m), 6.535 (1H, d, J = 6.6 Hz), 6.79 (1H, t, J = 7.4 Hz), 6.93 (2H, d, J = 7.8 Hz), 7.14-7.25 (2H, m), 7.50 (2H, dd, J = 6.9, 7.4 Hz).

(42c) 3-amino-4-(4-phenylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

4-(4-phenylpiperazin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 42 (42b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 75%.

Mp 250-252°C;

IR (KBr) $\nu_{max}$ 3438, 3318, 3176, 2832, 1645, 1596, 1579, 1447, 1377, 1343, 1238, 1136, 1135, 978, 914, 831, 762, 733, 693, 626, 484 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.89-3.71 (8H, br s), 6.70 (1H, t, J = 7.1 Hz), 6.93 (2H, s), 6.99 (2H, d, J = 9.0 Hz), 7.07 (2H, d, J = 5.5 Hz), 7.10 (2H, s), 7.22 (2H, dd, J = 7.4, 8.6 Hz), 8.44 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 353 $[M+H]^+$;

Anal. Calcd for $C_{18}H_{19}N_5OS \cdot 0.26H_2O$: C,60.37; H,5.49; N,19.56; S,8.95. Found: C, 60.18; H,5.33; N,19.55; S,9.02.

(Example 43) 3-amino-4-(4-benzylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-6)

(43a) (2Z)-3-(4-benzylpiperazin-1-yl) -2-cyanobut-2-enethioamide

1-benzylpiperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 33%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.25 (3H, s), 2.44 (4H, m), 3.37 (4H, m), 3.50 (2H, s), 7.22-7.34 (5H, m), 8.30 (1H, s), 8.98 (1H, s).

(43b) 4-(4-benzylpiperazin-4-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-3-(4-benzylpiperazin-1-yl)-2-cyanobut-2-enethioamide which was produced in Example 42 (42a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 78%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.49 (4H, m), 3.51 (2H, s), 3.61 (4H, m), 6.45 (1H, d, J = 7.8 Hz), 7.20-7.34 (5H, m), 7.50 (1H, d, J = 7.4 Hz).

(43c) 3-amino-4-(4-benzylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

4-(4-phenylpiperazin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 42 (42b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 75%.

Mp 241-242°C;

IR (KBr) $\nu_{max}$ 3435, 3398, 3322, 3128, 2828, 1656, 1585, 1503, 1452, 1373, 1348, 1250, 1232, 1132, 1061, 1009, 973, 826, 742, 699, 627, 551, 487 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.42-3.22 (8H, br s), 3.55 (1H, s), 6.89 (2H, s), 7.02 (1H, d, J = 5.5 Hz), 7.07 (2H, s), 7.20-7.34 (5H, s), 8.415 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 367 $[M+H]^+$;

Anal. Calcd for $C_{19}H_{21}N_5OS$: C,62.10; H,5.76; N,19.06; S,8.73. Found: C,61.96; H,5.63; N,18.76; S,8.75.

(Example 44) 3-amino-4-(4-pyrimidin-2-ylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-69)

(44a) (2Z)-2-cyano-3-(4-pyrimidin-2-ylpiperazin-1-yl)but-2-enethioamide

1-pyrimidin-2-ylpiperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 87%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.31 (3H, s), 3.51 (4H, m), 3.83 (4H, m), 6.66 (1H, t, J = 4.7 Hz), 8.32 (1H, s), 6.92 (2H, d, J = 4.7 Hz), 9.03 (1H, s).

(44b) 4-(4-pyrimidin-2-ylpiperazin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(4-pyrimidin-2-ylpiperazin-1-yl)but-2-enethioamide which was produced in Example 44 (44a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 77%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 3.785 (4H, m), 3.89 (4H, m), 6.53 (1H, d, J = 7.4 Hz), 6.69 (1H, t, J = 4.3 Hz), 7.52 (1H, t, J = 7.8 Hz), 7.50 (2H, d, J = 4.7 Hz), 12.74 (1H, br s).

(44c) 3-amino-4-(4-pyrimidin-2-ylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-(4-pyrimidin-2-ylpiperazin-1-yl)but-2-enethioamide which was produced in Example 44 (44b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 69%.

Mp 280°C (decomposition);

IR (KBr) $\nu_{max}$ 3439, 3317, 3141, 2835, 1648, 1582, 1548, 1500, 1466, 1359, 1241, 1133, 974, 797, 486 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.72-3.65 (8H, br s), 6.66 (1H, t, J = 4.7 Hz), 6.99 (2H, br s), 7.05 (2H, d, J = 5.1 Hz), 7.11 (2H, br s), 8.39 (2H, d, J = 4.7 Hz), 8.43 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 356 $[M+H]^+$;

Anal. Calcd for $C_{16}H_{17}N_7OS \cdot 0.24H_2O$: C,54.07; H,4.82; N,27.59; S,9.02. Found: C,53.59; H,4.81; N,27.03; S,8.99.

(Example 45) 3-amino-4-(4-pyridin-2-ylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-62)

(45a) (2Z)-2-cyano-3-(4-pyridin-2-ylpiperazin-1-yl)but-2-enethioamide

1-pyridin-2-ylpiperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 92%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.32 (3H, s), 3.53 (4H, m), 3.65 (4H, m), 6.67 (1H, t, J = 4.7 Hz), 6.83 (1H, d, J = 8.9 Hz), 7.57 (1H, t, J = 8.9 Hz), 8.14 (1H, d, J = 4.7 Hz), 8.36 (1H, br s), 9.07 (1H, br s).

(45b) 4-(4-pyridin-2-ylpiperazin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(4-pyridin-2-ylpiperazin-1-yl)but-2-enethioamide which was produced in Example 45 (45a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 43%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 3.70 (4H, m), 3.82 (4H, m), 6.53 (1H, d, J = 7.4 Hz), 6.72 (1H, t, J = 5.9 Hz), 6.90 (1H, d, J = 8.2 Hz), 7.52 (1H, t, J = 6.7 Hz), 7.64 (1H, t, J = 7.4 Hz), 8.13 (1H, d, J = 5.1 Hz), 12.73 (1H, br s).

(45c) 3-amino-4-(4-pyridin-2-ylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

4-(4-pyridin-2-ylpiperazin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 45 (45b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 77%.

Mp 266-270°C;

IR (KBr) $\nu_{max}$ 3438, 3317, 3142, 2834, 1674, 1590, 1582, 1501, 1435, 1369, 1345, 1133, 974, 774, 741, 620, 487 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.80-3.60 (8H, br s), 6.67 (1H, dd, J = 5.1, 6.3 Hz), 6.89 (1H, d, J = 8.2 Hz), 6.97 (2H, s), 7.06 (1H, d, J = 5.1 Hz), 7.11 (2H, s), 7.55 (1H, t, J = 5.1 Hz), 8.39 (1H, d, J = 3.5 Hz), 8.44 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 355 $[M+H]^+$;

Anal. Calcd for $C_{17}H_{18}N_6OS$: C,57.61; H,5.12; N,23.71; S,9.05. Found: C,57.25; H,5.01; N,23.35; S,9.04.

(Example 46) 3-amino-4-[4-(4-methylphenyl)piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-34)

(46a) (2Z)-2-cyano-3-[4-(4-methylphenyl)piperazin-1-yl]but-2-enethioamide

1-(4-methylphenyl)piperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 70%.

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.20 (3H, s), 2.30 (3H, s), 3.20 (4H, m), 3.51 (4H, m), 6.83 (2H, d, J = 8.6 Hz), 7.02 (2H, d, J = 8.2 Hz), 8.35 (1H, s), 9.04 (1H, s).

(46b) 4-[4-(4-methylphenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-[4-(4-methylphenyl)piperazin-1-yl]but-2-enethioamide which was produced in Example 46 (46a) was used in place of (2Z)-2-cyano-3-

(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 77%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.21 (3H, s), 3.22 (4H, m), 3.79 (4H, m), 6.45 (1H, d, J = 7.4 Hz), 6.86 (2H, d, J = 8.6 Hz), 7.05 (2H, d, J = 8.2 Hz), 7.52 (1H, t, J = 7.0 Hz), 12.73 (1H, br s).

(46c) 3-amino-4-[4-(4-methylphenyl)piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-methylphenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 46 (46b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 72%.

Mp 270°C (decomposition);

IR (KBr) $\nu_{max}$ 3433, 3310, 3143, 2829, 1667, 1611, 1580, 1513, 1449, 1371, 1345, 1237, 1134, 1124, 974, 956, 812, 617, 482 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.20 (3H, s), 2.91-3.60 (8H, br s), 6.86-7.12 (9H, m), 8.42 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 367 $[M+H]^+$;

Anal. Calcd for $C_{19}H_{21}N_5OS \cdot 0.24H_2O$: C,61.38; H,5.82; N,18.84; S,8.62. Found: C, 61.58; H,5.58; N,18.84; S,8.63.

(Example 47) 3-amino-4-[4-(4-fluorophenyl)piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-12)

(47a) (2Z)-2-cyano-3-[4-(4-fluorophenyl)piperazin-1-yl]but-2-enethioamide

1-(4-fluorophenyl) piperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 73%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.31 (3H, s), 3.21 (4H, m), 3.52 (4H, m), 6.83 (2H, dd, J = 4.7, 9.0 Hz), 7.02 (2H, t, J = 8.6 Hz), 8.37 (1H, s), 9.06 (1H, s).

(47b) 4-[4-(4-fluorophenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-[4-(4-fluorophenyl)piperazin-1-yl]but-2-enethioamide which was produced in Example 47 (47a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 74%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 3.24 (4H, m), 3.80 (4H, m), 6.56 (1H, d, J = 7.4 Hz), 6.98 (2H, dd, J = 4.7, 9.4 Hz), 7.08 (2H, t, J = 8.9 Hz), 7.52 (1H, d, J = 7.4 Hz).

(47c) 3-amino-4-[4-(4-fluorophenyl) piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-fluorophenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 47 (47b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 62%.

Mp 275°C (decomposition);

IR (KBr) $\nu_{max}$ 3443, 3324, 3180, 2832, 1646, 1583, 1558, 1509, 1450, 1373, 1345, 1234, 1136, 977, 959, 826, 716, 553 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.93-3.75 (8H, br s), 6.96 (2H, s), 7.00-7.19 (7H, m), 8.48 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 371 $[M+H]^+$;

Anal. Calcd for $C_{18}H_{18}FN_5OS \cdot 0.19H_2O$: C,57.67; H,4.94; N,18.68; S,8.55. Found: C, 57.72; H,4.72; N,18.58; S,8.53.

(Example 48) 3-amino-4-(4-benzhydrylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-7)

(48a) (2Z)-3-(4-benzhydrylpiperazin-1-yl)-2-cyanobut-2-enethioamide

1-benzhydrylpiperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 90%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.22 (3H, s), 2.38 (4H, m), 3.41 (4H, m), 4.34 (1H, s), 7.18 (2H, t, J = 7.4 Hz), 7.28 (4H, t, J = 7.8 Hz), 7.42 (4H, d, J = 7.0 Hz), 8.31 (1H, s), 8.98 (1H, s).

(48b) 4-(4-benzhydrylpiperazin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-3-(4-benzhydrylpiperazin-1-yl)-2-cyanobut-2-enethioamide which was produced in Example 48 (48a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 84%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.44 (4H, m), 3.66 (4H, m), 4.38 (1H, s), 6.47 (1H, d, J = 7.0 Hz), 7.23 (1H, d, J = 7.0 Hz), 7.27-7.66 (10H, m).

(48c) 3-amino-4-(4-benzhydrylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

4-(4-benzhydrylpiperazin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 48 (48b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 63%.

Mp 225-233°C;

IR (KBr) $\nu_{max}$ 3450, 3381, 3171, 2827, 1649, 1580, 1501, 1449, 1366, 1242, 1137, 979, 957, 835, 758, 706, 626, 473 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.20-3.40 (8H, br s), 4.38 (1H, s), 6.89 (1H, s), 7.07 (2H, m), 7.20 (2H, t, J = 7.4 Hz), 7.31 (5H, t, J = 7.4 Hz), 7.47 (5H, d, J = 7.4 Hz), 8.44 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 444 $[M+H]^+$;

Anal. Calcd for $C_{25}H_{25}N_5OS \cdot 0.26H_2O$: C,66.99; H,5.74; N,15.62; S,7.15. Found: C, 67.07; H,5.57; N,15.36; S,7.09.

(Example 49) 3-amino-4-[4-(4-methoxyphenyl)piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-47)

(49a) (2Z)-2-cyano-3-[4-(4-methoxyphenyl)piperazin-1-yl]but-2-enethioamide

1-(4-methoxyphenyl) piperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 73%.

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.31 (3H, s), 3.13 (4H, m), 3.52 (4H, m), 3.69 (3H, s), 6.84 (2H, d, J = 9.0 Hz), 6.92 (2H, d, J = 9.3 Hz), 8.39 (1H, s), 9.07 (1H, s).

(49b) 4-[4-(4-methoxyphenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-[4-(4-methoxyphenyl)piperazin-1-yl]but-2-enethioamide which was produced in Example 49 (49a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 59%.

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 3.14 (4H, m), 3.67 (3H, s), 3.77 (4H, m), 6.45 (1H, d, J = 7.1 Hz), 6.86 (2H, d, J = 9.4 Hz), 7.05 (2H, d, J = 9.4 Hz), 7.52 (1H, t, J = 7.4 Hz).

(49c) 3-amino-4-[4-(4-methoxyphenyl)-piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-methoxyphenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 49 (49b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 79%.

Mp 275°C (decomposition);

IR (KBr) $\nu_{max}$ 3435, 3311, 3160, 2957, 2831, 1664, 1609, 1511, 1449, 1373, 1346, 1242, 1182, 1136, 1035, 976, 959, 826, 740, 605, 480 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.95-3.56 (8H, br s), 3.69 (1H, s), 6.3 (1H, d, J = 9.0 Hz), 6.93 (2H, s), 6.95 (1H, d, J = 9.4 Hz), 7.07 (1H, d, J = 5.5 Hz), 7.09 (2H, s), 8.45 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 384 $[M+H]^+$;

Anal. Calcd for $C_{19}H_{21}N_5O_2S \cdot 0.28H_2O$: C,58.74; H,5.59; N,18.03; S,8.25. Found: C, 58.57; H,5.42; N,18.03; S,8.03.

(Example 50) 3-amino-4-{4-[(2E)-3-phenylprop-2-enyl]piperazin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-8)

(50a) (2Z)-2-cyano-3-{4-[(2E)-3-phenylpropane-2-enyl]piperazin-1-yl}but-2-enethioamide

1-[(2E)-3-phenylpropane-2-enyl]piperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 38%.

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.27 (3H, s), 2.50 (4H, m), 3.14 (2H, d, J = 5.9 Hz), 3.40 (4H, m), 3.69 (3H, s), 6.30 (1H, dt, J = 6.6, 16.0 Hz), 6.56 (1H, d, J = 16.0 Hz),

7.24 (1H, t, J = 7.4 Hz), 7.32 (2H, t, J = 7.0 Hz), 7.44 (2H, d, J = 7.0 Hz), 8.32 (1H, s), 9.01 (1H, s).

(50b) 4-{4-[(2E)-3-phenylpropane-2-enyl]piperazin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-{4-[(2E)-3-phenylpropane-2-enyl]piperazin-1-yl}but-2-enethioamide which was produced in Example 50 (50a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 84%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.85-4.44 (10H, m), 6.28 (1H, dt, J = 7.8, 14.8 Hz), 6.55 (1H, d, J = 7.4 Hz), 6.79 (1H, d, J = 14.9 Hz), 7.31 (1H, d, J = 7.4 Hz), 7.37 (2H, t, J = 7.4 Hz), 7.48 (2H, d, J = 7.4 Hz), 7.57 (1H, t, J = 6.7 Hz), 12.91 (1H, s).

(50c) 3-amino-4-{4-[(2E)-3-phenylprop-2-enyl]piperazin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

4-{4-[(2E)-3-phenylpropane-2-enyl]piperazin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 50 (50b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 60%.

Mp 225-227°C;

IR (KBr) $\nu_{max}$ 3433, 3319, 3184, 3024, 2832, 2811, 1649, 1578, 1501, 1448, 1369, 1347, 1129, 971, 823, 736, 693, 627, 470 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.42-3.81 (8H, br s), 3.19 (1H, d, J = 6.3 Hz), 6.32 (1H, dt, J = 6.6, 16.0 Hz), 6.55 (1H, d, J = 16.0 Hz), 6.90 (2H, s), 7.02 (1H, d, J = 5.0 Hz), 7.07 (2H, s), 7.21 (1H, t, J = 7.4 Hz), 7.30 (2H, t, J = 7.4 Hz), 7.43 (2H, d, J = 7.0 Hz), 8.41 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 394 $[M+H]^+$;

Anal. Calcd for $C_{21}H_{23}N_5OS \cdot 0.46H_2O$: C,62.78; H,6.00; N,17.43; S,7.98. Found: C, 62.45; H, 5.70; N,17.32; S,7.94.

(Example 51) 3-amino-4-(4-benzoylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-73)

3-amino-4-piperazin-1-ylthieno[2,3-b]pyridine-2-carboxamide dihydrochloride (99.7 mg, 0.28 mmol) which was produced in Example 38 was suspended in 1,4-dioxane (5 mL) and was blended with benzoyl chloride (37 μL, 0.31 mmol) and triethylamine (44 μL, 0.31 mmol) and the mixture was stirred for 12 hours. After evaporating the solvent, water (15 mL) was added and allowed to stand for several hours, a brown solid which was generated was filtrated, dried under vacuum and the title compound was obtained (31.8 mg, yield 29%).

Mp >300°C;

IR (KBr) $\nu_{max}$ 3437, 3325, 3182, 2923, 2856, 1635, 1598, 1567, 1495, 1411, 1284, 1244, 1013, 974, 720, 675, 482 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.95-3.66 (8H, br s), 6.99 (2H, s), 7.07 (1H, s), 7.15 (2H, s), 7.42-7.57 (3H, m), 7.96 (2H, m), 8.48 (1H, s);

MS (FAB) m/z: 382 $[M+H]^+$.

(Example 52) 3-amino-4-[4-(4-chlorophenyl)piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-17)

(52a) (2Z)-3-[4-(4-chlorophenyl)piperazin-1-yl]-2-cyanobut-2-enethioamide

1-(4-chlorophenyl) piperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 73%.

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.31 (3H, s), 3.29 (4H, m), 3.53 (4H, m), 6.95 (2H, d, J = 9.0 Hz), 7.25 (2H, d, J = 9.0 Hz), 8.39 (1H, s), 9.10 (1H, s).

(52b) 4-[4-(4-chlorophenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-3-[4-(4-chlorophenyl)piperazin-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 52 (52a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 74%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 3.31 (4H, m), 3.79 (4H, m), 6.52 (1H, d, J = 7.4 Hz), 6.93 (2H, d, J = 9.4 Hz), 7.23 (2H, d, J = 9.0 Hz), 7.50 (1H, m);

(52c) 3-amino-4-[4-(4-chlorophenyl) piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-chlorophenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 52 (52b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 50%.

Mp 297°C (decomposition);

IR (KBr) $\nu_{max}$ 3423, 3317, 3164, 2975, 2832, 1669, 1649, 1580, 1496, 1449, 1370, 1343, 1238, 1137, 1106, 976, 962, 819, 609, 487 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.95-3.66 (8H, br s), 6.94 (2H, s), 7.01 (2H, d, J = 9.0 Hz), 7.065 (1H, d, J = 5.1 Hz), 7.11 (2H, s), 7.25 (2H, d, J = 9.0 Hz), 8.445 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 388 $[M+H]^+$;

Anal. Calcd for $C_{18}H_{18}ClN_5OS$: C, 55.74; H, 4.68; N, 18.06; S, 8.27. Found: C, 55.43; H, 4.75; N, 17.98; S, 8.12.

(Example 53) 3-amino-4-[4-(2-methoxyphenyl)piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-45)

(53a) (2Z)-2-cyano-3-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-enethioamide

1-(2-methoxyphenyl) piperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 68%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.31 (3H, s), 3.05 (4H, m), 3.51 (4H, m), 3.80 (3H, s), 6.85-7.04 (4H, m), 8.39 (1H, s), 9.08 (1H, s).

(53b) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-enethioamide which was produced in Example 53 (53a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 76%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 3.08 (4H, m), 3.79 (7H, m), 6.44 (1H, d, J = 7.4 Hz), 6.86 (2H, s), 7.05 (2H, s), 7.49 (1H, t, J = 6.6 Hz), 12.96 (1H, s).

(53c) 3-amino-4-[4-(2-methoxyphenyl) piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(2-methoxyphenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 53 (53b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 71%.

Mp 294°C (decomposition);

IR (KBr) $\nu_{max}$ 3435, 3311, 3160, 2957, 2831, 1664, 1609, 1511, 1449, 1373, 1346, 1242, 1182, 1136, 1035, 976, 959, 826, 740, 605, 480 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.96-3.56 (8H, br s), 3.79 (3H, s), 6.86-7.00 (6H, m), 7.10 (3H, d, J = 5.1 Hz), 8.445 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 384 $[M+H]^+$;

Anal. Calcd for $C_{19}H_{21}N_5O_2S \cdot 0.1H_2O$: C, 59.23; H, 5.55; N, 18.18; S,8.32. Found: C, 58.94; H, 5.25; N, 18.29; S, 8.21.

(Example 54) 3-amino-4-[4-(2-chlorophenyl)piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-15)

(54a) (2Z)-3-[4-(2-chlorophenyl)piperazin-1-yl]-2-cyanobut-2-enethioamide

1-(2-chlorophenyl) piperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 71%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.31 (3H, s), 3.05 (4H, m), 3.51 (4H, m), 3.80 (3H, s), 6.85-7.04 (4H, m), 8.39 (1H, s), 9.08 (1H, s).

(54b) 4-[4-(2-chlorophenyl)-piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-3-[4-(2-chlorophenyl)piperazin-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 54 (54a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 1 (1b) and the title compound was obtained. Yield 37%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 3.11 (4H, m), 3.79 (4H, m), 6.44 (1H, d, J = 7.4 Hz), 7.06 (1H, t, J = 7.4 Hz), 7.16 (1H, d, J = 7.8 Hz), 7.30 (1H, t, J = 7.4 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.51 (1H, t, J = 7.0 Hz).

(54c) 3-amino-4-[4-(2-chlorophenyl) piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(2-chlorophenyl)-piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 54 (54b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 79%.

Mp 294-298°C (decomposition);

IR (KBr) $\nu_{max}$ 3449, 3327, 3131, 2842, 1665, 1606, 1581, 1501, 1447, 1375, 1284, 1245, 1230, 1182, 1135, 1038, 976, 957, 826, 766, 627, 483 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.95-3.62 (8H, br s), 6.98 (2H, s), 7.03-7.14 (4H, m), 7.25 (1H, d, J = 7.8 Hz), 7.33 (1H, t, J = 7.0 Hz), 7.42 (1H, d, J = 7.8 Hz), 8.45 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 388 $[M+H]^+$;

Anal. Calcd for $C_{18}H_{18}ClN_5OS$: C, 55.74; H, 4.68; N, 18.06; S, 8.27. Found: C, 55.48; H, 4.75; N, 17.95; S, 8.04.

(Example 55) tert-butyl 4-[3-amino-2-(aminocarbonyl)thieno[2,3-b]pyridin-4-yl]-1,4-diazepane-1-carboxylate (Exemplified Compound No. 3-152)

(55a) tert-butyl 4-[(1Z)-3-amino-2-cyano-1-methyl-3-thiooxoprop-1-enyl]-1,4-diazepane-1-carboxylate]

N-Boc-homopiperazine was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Yellow powder

Mp 189-190°C;

IR (KBr) $\nu_{max}$ 3284, 3196, 2188, 1686, 1526, 1415, 1280, 1167, 884 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.38 (9H, s), 1.75-1.82 (2H, m), 2.27 (3H, s), 3.29-3.52 (8H, m), 8.80 (1H, brs), 9.02 (1H, brs);

HRMS m/z calcd for $C_{15}H_{25}O_2N_4S$ 325.1798, found 325.1715;

MS (FAB) m/z: 325 [$M^+$], 269, 252, 235, 201, 191, 65, 57;

Anal. Calcd for $C_{15}H_{24}N_4O_2S$: C, 55.53; H, 7.46; N, 12.27; S, 9.88. Found: C, 55.40; H, 7.48; N, 17.15, S, 9.68.

(55b) tert-butyl 4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepane-1-carboxylate

tert-butyl 4-[(1Z)-3-amino-2-cyano-1-methyl-3-thiooxoprop-1-enyl]-1,4-diazepane-1-carboxylate] which was produced in Example 55 (55a) was used in place of (2Z)-2-cyano-3-(isobutylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 5 (5b), and the title compound was obtained.

White powder

Mp 203-205°C;

IR (KBr) $\nu_{max}$ 2974, 2205, 1692, 1625, 1537, 1478, 1246, 1152, 929, 771 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.27 (4.5 H, s), 1.33 (4.5 H, s), 1.71-1.85 (2H, m), 3.31-3.38 (2H, m), 3.50-3.60 (2H, m), 3.74-3.84 (2H, m), 3.87-4.04 (2H, m), 6.42 (1H, t, J = 7.4 Hz), 7.88 (1H, d, J = 7.4 Hz), 12.44 (1H, brs);

HRMS m/z calcd for $C_{16}H_2O_2N_4S$ 335.1542, found 335.1541;

MS (FAB) m/z: 335 $[M+H]^+$, 289, 279, 233, 200, 176, 165, 93, 83;

Anal. Calcd for $C_{16}H_{22}N_4O_2S$: C, 57.46; H, 6.63; N, 16.75; S, 9.59. Found: C, 57.10; H, 6.24; N, 16.66, S, 9.82.

(55c) tert-butyl 4-[3-amino-2-(aminocarbonyl)thieno[2,3-b]pyridin-4-yl]-1,4-diazepane-1-carboxylate

tert-butyl 4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepane-1-carboxylate which was produced in Example 55 (55b) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was

performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Pale yellow powder

Mp 177-178°C;

IR (KBr) $\nu_{max}$ 3431, 3316, 3145, 2973, 1686, 1581, 1502, 1411, 1366, 1170, 929, 769 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.40 (4.5H, s), 1.43 (4.5H, s), 1.93-2.02 (2H, m), 3.17-3.23 (4H, m), 3.47 (2H, t, J = 6.3 Hz), 3.58-3.63 (2H, m), 7.00 (2H, brs), 7.06 (1H, d, J = 5.1 Hz), 7.08 (2H, brs), 8.39 (1H, d, J = 5.1 Hz);

HRMS m/z calcd for $C_{18}H_{26}O_3N_5S$ 392.1757, found 392.1761;

MS (FAB) m/z: 391 [$M^+$], 336, 319, 289, 230, 218, 202, 190, 176, 93;

Anal. Calcd for $C_{18}H_{25}N_5O_3S$: C, 55.22; H, 6.44; N, 17.89; S, 8.19. Found: C, 54.90; H, 6.40; N, 17.85; S, 8.26.

(Example 56) 3-amino-4-(4-benzyl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-83)

(56a) (2Z)-3-(4-benzyl-1,4-diazepan-1-yl)-2-cyanobut-2-enethioamide

1-benzylhomopiperazine was used in place of propylamine, the reaction was performed in a similar method as described in Example 4 (4a) and the title compound was obtained. Yield 88%.

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.86 (2H, m), 2.30 (3H, s), 2.57 (2H, t, J = 5.1 Hz), 2.67-2.73 (2H, m), 3.50-3.54 (4H, m), 3.57, (2H, s), 7.21-7.32 (5H, m), 8.18 (1H, s), 8.84 (1H, s).

(56b) 4-(4- benzyl-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-3-(4-benzyl-1,4-diazepan-1-yl)-2-cyanobut-2-enethioamide which was produced in Example 56 (56a) was used in place of (2Z)-2-cyano-3-(dimethylamino)but-2-enethioamide and the reaction was performed in a similar

method as described in Example 1 (1b) and the title compound was obtained. Yield 70%.

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.80-4.43 (12H, m), 6.38 (1H, d, J = 7.4 Hz), 7.15-7.61 (6H, m).

(56c) 3-amino-4-(4-benzyl-1,4-diazepan-1-yl)thieno [2,3-b]pyridine-2-carboxamide

4-(4-benzyl-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 56 (56b) was used in place of 4-(dimethylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 1 (1c) and the title compound was synthesized. Yield 75%.

Mp 194-195°C;

IR (KBr) $\nu_{max}$ 3429, 3306, 3142, 2937, 2828, 1674, 1646, 1583, 1501, 1452, 1368, 1344, 1262, 1157, 1108, 1026, 925, 740, 699, 483 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.86 (2H, m), 2.70 (2H, m), 2.79 (2H, m), 3.29 (2H, m), 3.35 (2H, m), 3.67 (2H, s), 7.04 (2H, s), 7.06 (2H, s), 7.15 (2H, s), 7.25 (1H, m), 7.31-7.37 (4H, m), 8.365 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 382 $[M+H]^+$;

Anal. Calcd for $C_{20}H_{23}N_5OS$: C, 62.97; H, 6.08; N, 18.36; S, 8.41. Found: C, 62.94; H, 5.75; N, 18.33; S, 8.30.

(Example 57) 3-amino-4-(4-phenyl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-86)

(57a) tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate

The title compound was synthesized by performing a reaction in a similar method as described in Org.Lett.,4,581-584(2002).

Brown liquid

IR (film) $\nu_{max}$ 2974, 1694, 1599, 1506, 1415, 1237, 1169, 930, 748, 692 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.37 (4.5H, s), 1.44 (4.5H, s), 1.93-2.00 (2H, m), 3.19 (1H, t, J = 5.9 Hz), 3.80 (1H, t, J = 5.9 Hz), 3.51-3.57 (6H, m), 6.63-6.69 (3H, m), 7.19 (2H, t, J = 7.1 Hz);

HRMS m/z calcd for $C_1H_{24}O_2N_2$ 276.1835, found 276.1833;

MS (EI) m/z: 276 [$M^+$], 220, 205, 175, 146, 132, 120, 94, 57;

Anal. Calcd for $C_{16}H_{24}N_2O_2 \cdot 0.14H_2O$: C, 68.90; H, 8.77; N, 10.04. Found: C, 68.96; H, 8.75; N, 9.85.

(57b) 1-phenyl-1,4-diazepane

4N hydrochloric acid-dioxane solution (75 mL) was added to methanol (20 mL) solution of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate (16.58 g, 60.0 mmol) which was produced in Example 57 (57a) and the mixture was stirred at room temperature for one hour. The reaction liquid was concentrated, and a sodium hydrogen carbonate aqueous solution (100 mL) was added to the obtained residual substance, and extracted with a mixed solvent (3x100 mL) of methylene chloride/2-methylene chloride propanol (4:1) and after the extracted solvent was dried over sodium sulfate, the solvent was evaporated under reduced pressure and the title compound (10.57 g, yield 100%) was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2931, 1598, 1506, 1394, 1245, 1035, 748, 692 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 500 MHz) δ 1.87-1.92 (2H, m), 2.83 (2H, t, J = 5.9 Hz), 3.03 (2H, t, J = 5.9 Hz), 3.54-3.59 (4H, m), 6.65 (1H, t, J = 8.3 Hz), 6.70 (2H, d, J = 8.3 Hz), 7.21 (2H, t, J = 8.3 Hz);

HRMS m/z calcd for $C_{11}H_{16}N_2$ 176.1313, found 176.1318;

MS (EI) m/z: 176 [$M^+$], 146, 134, 120, 106, 94, 77, 69, 43.

(57c) (2Z)-2-cyano-3-(4-phenyl-1,4-diazepan-1-yl)but-2-enethioamide

1-phenyl-1,4-diazepane which was produced in Example 57 (57b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 151-153°C;

IR (KBr) $\nu_{max}$ 3290, 2185, 1599, 1538, 1503, 1397, 1369, 1011, 873, 754 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.91-1.96 (2H, m), 2.23 (3H, s), 3.50-3.55 (4H, m), 3.61-3.63 (2H, m), 3.71-3.73 (2H, m), 6.61 (1H, t, J = 7.3 Hz), 6.76 (2H, d, J = 7.3 Hz), 7.16 (2H, t, J = 7.3 Hz), 8.33 (1H, brs), 9.00 (1H, brs);

HRMS m/z calcd for $C_{16}H_{21}N_4S$ 301.1487, found 301.1465;

MS (FAB) m/z: 300 [$M^+$], 267, 242, 195, 175;

Anal. Calcd for $C_{16}H_{20}N_4S$: C, 63.97; H, 6.71; N, 18.65; S, 10.67. Found: C, 63.76; H, 6.47; N, 18.75, S, 10.62.

(57d) 4-(4-phenyl-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(4-phenyl-1,4-diazepan-1-yl)but-2-enethioamide was used in place of (2Z)-2-cyano-3-(isobutylamino)but-2-enethioamide which was produced in Example 57 (57c) and the reaction was performed in a similar method as described in Example 5 (5b) and the title compound was synthesized.

Brown powder

Mp 128-132°C;

IR (KBr) $\nu_{max}$ 2954, 2205, 1626, 1504, 1248, 1136, 928, 750, 617 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.90-1.96 (2H, m), 3.51 (2H, t, J = 5.9 Hz), 3.71 (4H, q, J = 5.9 Hz), 3.93 (2H, t, J = 5.9 Hz), 6.40 (1H, d, J = 7.4 Hz), 6.56 (1H, t, J = 7.1 Hz), 6.74 (2H, d, J = 7.1 Hz), 7.12 (2H, t, J = 7.1 Hz), 7.83 (1H, d, J = 7.4 Hz), 12.47 (1H, brs);

HRMS m/z calcd for $C_{17}H_{18}N_4S$ 310.1252, found 310.1224;

MS (EI) m/z: 310 [$M^+$], 281, 251, 204, 165, 132;

Anal. Calcd for $C_{17}H_{18}N_4S$: C, 65.78; H, 5.84; N, 18.05; S, 10.33. Found: C, 65.58; H, 5.51; N, 18.03, S, 10.24.

(57e) 3-amino-4-(4-phenyl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

4-(4-phenyl-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 57 (57d) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was synthesized.

White powder

Mp 215-218°C;

IR (KBr) $\nu_{max}$ 3340, 3316, 3143, 1645, 1598, 1504, 1369, 1233, 939, 752, 694 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.10-2.15 (2H, m), 3.16-3.19 (2H, m), 3.26-3.29 (2H, m), 3.52 (2H, t, J = 6.3 Hz), 3.75 (2H, t, J = 6.3 Hz), 6.58 (1H, t, J = 8.2 Hz), 6.74 (2H, d, J = 8.2 Hz), 6.95 (2H, brs), 7.05 (1H, d, J = 5.5 Hz), 7.05 (2H, brs), 7.14 (2H, t, J = 8.2 Hz), 8.36 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{19}H_{21}N_5OS$ 367.1467, found 367.1462;

MS (EI) m/z: 367 [$M^+$], 335, 324, 275, 259, 242, 216, 202, 175, 146, 120;

Anal. Calcd for $C_{19}H_{21}N_5OS \cdot 0.24H_2O$: C, 61.38; H, 5.82; N, 18.84; S, 8.62. Found: C, 61.22; H, 5.64; N, 18.94; S, 8.49.

(Example 58) 3-amino-4-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-124)

(58a) tert-butyl 4-(4-methoxyphenyl)-1,4-diazepane-1-carboxylate

The title compound was synthesized by performing a reaction in a similar method as described in Org.Lett.,4,581-584(2002).

Brown liquid

IR (film) $\nu_{max}$ 2974, 1693, 1513, 1415, 1242, 1169, 1041, 930, 815 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 500 MHz) δ 1.37 (4.5H, s), 1.44 (4.5H, s), 1.92-1.99 (2H, m), 3.20 (1H, t, J = 5.9 Hz), 3.31 (1H, t, J = 5.9 Hz), 3.47-3.57 (6H, m), 3.74 (3H, s), 6.65 (2H, d, J = 9.3 Hz), 6.81 (2H, d, J = 9.3 Hz);

HRMS m/z calcd for $C_{17}H_{26}O_3N_2$ 306.1943, found 306.1935;

MS (EI) m/z: 306 [$M^+$], 250, 235, 205, 189, 162, 150, 121, 70, 57;

Anal. Calcd for $C_{17}H_{26}N_2O_3 \cdot 0.36H2O$: C, 65.26; H, 8.61; N, 8.95. Found: C, 64.92; H, 8.29; N, 8.87.

(58b) 1-(4-methoxyphenyl)-1,4-diazepane

tert-butyl 4-(4-methoxyphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 58 (58a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2934, 1513, 1241, 1040, 814 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.89 (2H, quint, J = 5.1 Hz), 2.89 (2H, t, J = 5.1 Hz), 3.02 (2H, t, J = 5.1 Hz), 3.48-3.54 (4H, m), 3.75 (3H, s), 6.65 (2H, d, J = 9.0 Hz), 6.82 (2H, d, J = 9.0 Hz);

HRMS m/z calcd for $C_{12}H_{18}ON_2$ 206.1419, found 206.1424;

MS (EI) m/z: 206 [$M^+$], 176, 164, 150, 136, 121, 109, 92, 77, 70, 43.

(58c) (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(4-methoxyphenyl)-1,4-diazepane which was produced in Example 58 (58b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 157-158°C;

IR (KBr) $\nu_{max}$ 3284, 3154, 2179, 1512, 1361, 1243, 1037, 821 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.89-1.96 (2H, m), 2.24 (3H, s), 3.44 (2H, t, J = 5.9 Hz), 3.49 (2H, t, J =5.9 Hz), 3.57-3.63 (4H, m), 3.64 (3H, s), 6.70 (2H, d, J = 9.0 Hz), 6.76 (2H, d, J = 9.0 Hz), 8.27 (1H, brs), 8.95 (1H, brs);

HRMS m/z calcd for $C_{17}H_{23}ON_4S$ 331.1593, found 331.1589;

MS (FAB) m/z: 331 $[M+H]^+$, 246, 228, 182, 63;

Anal. Calcd for $C_{17}H_{22}N_4OS$: C, 61.79; H, 6.71; N, 16.95; S, 9.70. Found: C, 61.51; H, 6.69; N, 16.99, S, 9.71.

(58d) (2Z)-2-cyano-N-[(1E)-(dimethylamino) methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide

(2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide (476 mg, 1.44 mmol) which was produced in Example 58 (58c) was suspended in ethanol (15 mL) and was blended with N,N-dimethylformamide dimethylacetal (382 μL, 2.88 mmol) and the mixture was stirred at room temperature for one day. After the deposited solid was washed with ethanol, the title compound (452 mg, yield 81%) was obtained.

Yellow powder

Mp 145-146°C;

IR (KBr) $\nu_{max}$ 2926, 2178, 1610, 1512, 1324, 1294, 1187, 1012, 923, 669, 514 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.94-2.00 (2H, m), 2.50 (3H, s), 2.93 (3H, s), 3.14 (3H, s), 3.45-3.49 (2H, m), 3.65 (3H, s), 3.69-3.79 (6H, m), 6.73 (2H, d, J = 7.8 Hz), 6.78 (2H, d, J = 7.8 Hz), 8.46 (1H, s);

HRMS m/z calcd for $C_{20}H_{28}ON_5S$ 386.2014, found 386.2007;

MS (FAB) m/z: 386 $[M+H]^+$, 369, 352, 273, 242, 196, 165, 65, 55;

Anal. Calcd for $C_{20}H_{27}N_5OS$: C, 62.31; H, 7.06; N, 18.17; S, 8.32. Found: C, 62.03; H, 6.88; N, 18.02; S, 8.50.

(58e) 3-amino-4-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

N,N-dimethylformamide (2.3 mL) solution of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide (443 mg, 1.15 mmol) which was produced in Example 58 (58d) was stirred at 80°C for one hour. The reaction liquid was cooled to room temperature and was blended with 2-chloroacetamide (129 mg, 1.38 mmol) and 8M aqueous solution of sodium hydroxide (0.49 mL) and the mixture was stirred at room temperature for one hour.

Water (5 mL) was added to the reaction liquid and the resulted solid was separated by filtration and the title compound (378 mg, yield 83%) was obtained.

Pale yellow powder

Mp 206-208°C;

IR (KBr) $\nu_{max}$ 3446, 3328, 3168, 1578, 1511, 1370, 1240, 1037, 937, 816 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.78-1.86 (2H, m), 2.89-2.95 (2H, m), 2.97-3.01 (2H, m), 3.19 (2H, t, J = 5.9 Hz), 3.37 (3H, s), 3.37-3.42 (2H, m), 6.43 (2H, d, J = 9.4 Hz), 6.51 (2H, d, J = 9.4 Hz), 6.69 (2H, brs), 6.77-6.79 (2H, m), 8.10 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{20}H_{24}O_2N_5S$ 398.1651, found 398.1635;

MS (FAB) m/z: 398 $[M+H]^+$, 273, 257, 242, 226, 200, 165, 63;

Anal. Calcd for $C_{20}H_{23}N_5O_2S \cdot 0.52H_2O$: C, 59.04; H, 5.96; N, 17.21. Found: C, 58.73; H, 6.09; N, 17.52.

(Example 59) 3-amino-4-[4-(4-nitrophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-97)

(59a) tert-butyl 4-(4-nitrophenyl)-1,4-diazepane-1-carboxylate

4-fluoro nitrobenzene (282 mg, 2 mmol) and tert-butoxycarbonyl homopiperazine (801 mg, 4 mmol) were dissolved in dimethylsulfoxide (5 mL) and the mixture was stirred at 80°C for one hour. Ethyl acetate (20 mL) and water (20

mL) was added to the reaction liquid and, after partitioning, the organic layer was washed with water (20 mLx5) and a saline solution (20 mL), and after drying over sodium sulfate, the solvent was evaporated under reduced pressure. After the obtained residue was blended with hexane and solidified, it was separated by filtration and purified and the title compound (620 mg, yield 96%) was obtained.

Yellow powder

IR (KBr) $\nu_{max}$ 1683, 1600, 1482, 1422, 1310, 1253, 1114, 983, 824 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.16 (4.5H, s), 1.27 (4.5H, s), 1.71-1.83 (2H, m), 3.22 (1H, t, J = 5.5 Hz), 3.29 (1H, t, J = 7.4 Hz), 3.50 (1H, t, J = 5.9 Hz), 3.56 (1H, t, J = 5.9 Hz), 3.62-3.65 (2H, m), 3.70-3.77 (2H, m), 6.87 (2H, d, J = 9.4 Hz), 8.00-8.04 (2H, m);

HRMS m/z calcd for $C_{16}H_{23}N_3O_4$ 321.1689, found 321.1682;

MS (FAB) m/z: 321 [$M^+$], 266, 220, 200, 120.

(59b) 1-(4-nitrophenyl)-1,4-diazepane

tert-butyl 4-(4-nitrophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 59 (59a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.71-1.77 (2H, m), 2.61 (2H, t, J = 5.9 Hz), 2.83 (2H, t, J = 5.9 Hz), 3.56 (2H, t, J = 5.9 Hz), 3.63 (2H, t, J = 5.9 Hz), 6.79 (2H, d, J = 9.4 Hz), 7.99 (2H, d, J = 9.4 Hz).

(59c) (2Z)-2-cyano-3-[4-(4-nitrophenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(4-nitrophenyl)-1,4-diazepane which was produced in Example 59 (59b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Yellow powder

IR (KBr) $\nu_{max}$ 3190, 2183, 1596, 1516, 1315, 1115 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.91-1.96 (2H, m), 2.22 (3H, s), 3.54-3.57 (2H, m), 3.52-3.65 (2H, m), 3.69-3.72 (2H, m), 3.90-3.92 (2H, m), 6.91 (2H, d, J = 8.2 Hz), 8.03 (2H, d, J = 8.2 Hz), 8.45 (1H, brs), 9.08 (1H, brs);

HRMS m/z calcd for $C_{16}H_{20}O_2N_5S$ 346.1337, found 346.1342;

MS (FAB) m/z: 346 $[M+H]^+$, 329, 273, 200, 165.

(59d) 4-[4-(4-nitrophenyl)-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-[4-(4-nitrophenyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 59 (59c) was used in place of (2Z)-2-cyano-3-(isobutylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 5 (5b) and the title compound was obtained.

Brown powder

IR (KBr) $\nu_{max}$ 2204, 1596, 1515, 1312, 1114, 927, 752 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.91-1.97 (2H, m), 3.65-3.70 (2H, m), 3.75-3.78(2H, m), 3.88-3.90 (2H, m), 3.97-3.99 (2H, m), 6.43 (1H, d, J = 7.8 Hz), 6.92 (1H, t, J = 9.4 Hz), 7.86 (1H, d, J = 7.8 Hz), 8.01 (2H, d, J = 9.4 Hz);

HRMS m/z calcd for $C_{17}H_{18}N_5O_2S$ 356.1182, found 356.1165;

MS (EI) m/z: 356 $[M+H]^+$, 273, 246, 182, 120.

(59e) 3-amino-4-[4-(4-nitrophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-nitrophenyl)-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 59 (59d) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Yellow powder

Mp 244-248°C;

IR (KBr) $\nu_{max}$ 3439, 1646, 1596, 1509, 1312, 1114, 824, 7534 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.17-2.23 (2H, m), 3.18-3.24 (2H, m), 3.31-3.36 (2H, m), 3.72 (2H, t, J = 5.9 Hz), 3.91-3.95 (2H, m), 6.93 (2H, d, J = 9.4 Hz), 7.00 (2H, brs), 7.08 (1H, d, J = 5.5 Hz), 7.12 (2H, brs), 8.07 (2H, t, J = 9.4 Hz), 8.41 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{19}H_{21}N_6O_3S$ 413.1396, found 413.1400;

MS (FAB) m/z: 413 $[M+H]^+$, 338, 246, 182;

Anal. Calcd for $C_{19}H_{20}N_6O_3S \cdot 0.76H_2O$: C, 53.55; H, 5.09; N, 19.72; S, 7.52. Found: C, 53.85; H, 4.86; N, 19.54, S, 7.14.

(Example 60) 3-amino-4-[4-(4-chlorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-94)

(60a) tert-butyl 4-(4-chlorophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

Brown liquid

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.36 (4.5H, s), 1.43 (4.5H, s), 1.91-1.97 (2H, m), 3.19 (1H, t, J = 6.3 Hz), 3.30 (1H, t, J = 6.3 Hz), 3.48-3.56 (6H, m), 6.59 (2H, d, J = 9.0 Hz), 7.121 (2H, d, J = 3.5, 9.0 Hz).

(60b) 1-(4-chlorophenyl)-1,4-diazepane

tert-butyl 4-(4-chlorophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 60 (60a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.87 (2H, quint, J = 5.9 Hz), 2.80 (2H, t, J = 5.9 Hz), 3.00 (2H, t, J = 5.9 Hz), 3.49 (2H, t, J = 5.9 Hz), 3.53 (2H, t, J = 5.9 Hz), 6.58 (2H, t, J = 9.4 Hz), 7.11 (2H, d, J = 9.4 Hz).

(60c) (2Z)-3-[4-(4-chlorophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide

1-(4-chlorophenyl)-1,4-diazepane which was produced in Example 60 (60b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 170-172°C (decomposition);

IR (KBr) $\nu_{max}$ 3370, 3268, 3175, 2187, 1536, 1498, 1397, 813, 510 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.88-1.94 (2H, m), 2.22 (3H, s), 3.48-3.53 (4H, m), 3.58-3.60 (2H, m), 3.70-3.72 (2H, m), 6.75 (2H, d, J = 9.0 Hz), 7.14 (2H, d, J = 9.0 Hz), 8.34 (1H, brs), 8.98 (1H, brs);

HRMS m/z calcd for $C_{16}H_{20}N_4ClS$ 335.1097, found 335.1095;

MS (FAB) m/z: 335 $[M+H]^+$, 273, 246, 211, 165, 63;

Anal. Calcd for $C_{16}H_{19}ClN_4S$: C, 57.39; H, 5.47; N, 16.73; Cl, 10.59; S, 9.58. Found: C, 57.23; H, 5.47; N, 17.77; Cl, 10.59; S, 9.54.

(60d) (2Z)-3-[4-(4-chlorophenyl)-1,4-diazepan-1-yl]-2-cyano-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide

(2Z)-3-[4-(4-chlorophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 60 (60c) was used in place of (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Yellow powder

Mp 259-264°C;

IR (KBr) $\nu_{max}$ 2926, 2176, 1610, 1499, 1328, 1291, 1194, 1012, 923, 820 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.94-1.97 (2H, m), 2.46 (3H, s), 2.90 (3H, s) 3.13 (3H, s), 3.54 (2H, t, J = 5.9 Hz), 3.69-3.76(4H, m), 3.79-3.81 (2H, m), 6.75 (2H, d, J = 9.0 Hz), 7.11 (2H, d, J = 9.0 Hz), 8.42 (1H, s);

HRMS m/z calcd for $C_{19}H_{25}N_5ClS$ 390.1519, found 390.1524;

MS (FAB) m/z: 390 $[M+H]^+$, 356, 318, 273, 208, 196, 180, 166, 90;

Anal. Calcd for $C_{19}H_{24}ClN_5S$: C, 58.42; H, 6.20; N, 17.96; Cl, 9.09; S, 8.22. Found: C, 58.41; H, 6.17; N, 17.66, Cl, 8.91; S, 8.12.

(60e) 3-amino-4-[4-(4-chlorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-3-[4-(4-chlorophenyl)-1,4-diazepan-1-yl]-2-cyano-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide which was produced in Example 60 (60d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

Pale yellow powder

Mp 92-96°C;

IR (KBr) $\nu_{max}$ 3441, 3323, 2948, 1646, 1594, 1499, 1368, 939, 810 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 2.11-2.16 (2H, m), 3.15-3.20 (2H, m), 3.26-3.28 (2H, m), 3.53 (2H, t, J = 5.9 Hz), 3.75 (2H, t, J = 4.4 Hz), 6.76 (2H, d, J = 8.8 Hz), 6.99 (2H, brs), 7.07 (1H, d, J = 5.4 Hz), 7.08 (2H, brs), 7.17 (2H, t, J = 8.8 Hz), 8.40 (1H, d, J = 5.4 Hz);

HRMS m/z calcd for $C_{19}H_{21}N_5OClS$ 402.1155, found 402.1158;

MS (FAB) m/z: 402 $[M+H]^+$, 385, 273, 258, 246, 211, 200, 93;

Anal. Calcd for $C_{19}H_{20}ClN_5OS \cdot 0.51H_2O$: C, 55.51; H, 5.15; N, 17.04; Cl, 8.62. Found: C, 55.60; H, 5.09; N, 16.84; Cl, 8.76.

(Example 61) 3-amino-4-[4-(2-chlorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-92)

(61a) tert-butyl 4-(2-chlorophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Brown liquid

IR (film) $\nu_{max}$ 2976, 1692, 1482, 1366, 1160, 751 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.46 (4.5H, s), 1.47 (4.5H, s), 1.97-2.04 (2H, m), 3.14-3.21 (4H, m), 3.53-3.64 (4H, m), 6.90 (1H, t, J = 7.1 Hz), 7.04 (1H, d, J = 7.1 Hz), 7.14 (1H, t, J = 7.1 Hz), 7.32 (1H, d, J = 7.1 Hz);

HRMS m/z calcd for $C_{16}H_{23}N_2O_2{}^{35}Cl$ 310.1448, found 310.1472;

MS (EI) m/z: 310 [$M^+$], 282, 253, 237, 209, 193, 180, 166, 154, 138, 125, 111, 70, 57.

(61b) 1-(2-chlorophenyl)-1,4-diazepane

tert-butyl 4-(2-chlorophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 61 (61a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2941, 2836, 1588, 1481, 1295, 1040, 752 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.93 (2H, quint, J = 5.9 Hz), 2.18 (1H, brs), 3.03-3.08 (4H, m), 3.23-3.29 (4H, m), 6.87 (1H, t, J = 5.9 Hz), 7.07 (1H, d, J = 5.9 Hz), 7.14 (1H, t, J = 5.9 Hz), 7.31 (1H, d, J = 5.9 Hz);

HRMS m/z calcd for $C_{11}H_{15}N_2Cl$ 210.0924, found 210.0916;

MS (EI) m/z: 210 [$M^+$], 180, 175, 168, 154, 146, 128, 111, 92, 77, 64.

(61c) (2Z)-3-[4-(2-chlorophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide

1-(2-chlorophenyl)-1,4-diazepane which was produced in Example 61 (61b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 123-124°C;

IR (KBr) $\nu_{max}$ 3367, 3265, 3186, 2184, 1611, 1525, 1402, 1289, 1041, 766, 673 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 2.12-2.17 (2H, m), 2.69 (3H, s), 3.23 (2H, t, J = 5.9 Hz), 3.34-3.37 (2H, m), 3.91 (2H, t, J = 5.9 Hz), 3.97-4.00 (2H, m), 6.70 (2H, brs), 6.97 (1H, dt, J = 1.2, 8.2 Hz), 7.05 (1H, dd, J = 1.2, 8.2 Hz), 7.19 (1H, dt, J = 1.2, 8.2 Hz), 7.35 (1H, dd, J = 1.2, 8.2 Hz);

HRMS m/z calcd for $C_{16}H_{20}N_4ClS$ 335.1097, found 335.1098;

MS (FAB) m/z: 335 $[M+H]^+$, 273, 246, 211;

Anal. Calcd for $C_{16}H_{19}ClN_4S \cdot 0.64H_2O$: C, 55.48; H, 5.90; N, 16.17; Cl, 10.23; S, 9.26. Found: C, 55.69; H, 5.81; N, 16.19; Cl, 9.97; S, 9.35.

(61d) 3-amino-4-[4-(2-chlorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-3-[4-(2-chlorophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide (64 mg, 0.19 mmol) which was produced in Example 61 (61c) and N,N-dimethylformamide dimethylacetal (54 mg, 0.45 mmol) were dissolved in ethanol (2 mL) and after stirring at room temperature for one hour, the solvent was evaporated. The residue was dissolved in N,N-dimethylformamide (0.3 mL) and the mixture was stirred at 80°C for 15 minutes. The reaction mixture was cooled to room temperature and 8N aqueous solution of sodium hydroxide (0.08 mL) and 2-chloroacetamide (21 mg, 0.22 mmol) were added. After stirring at room temperature one hour, the reaction mixture was partitioned with water and ethyl acetate and the organic solvent was concentrated under reduced pressure after drying over sodium sulfate. A solid was separated by filtration after the residue was

solidified with hydrous ethanol and the title compound was obtained 76 mg (yield 31%).

Pale yellow powder

Mp 206-210°C;

IR (KBr) $\nu_{max}$ 3435, 3318, 3168, 1645, 1584, 1501, 1369, 1041, 937, 761 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.05-2.11 (2H, m), 3.28-3.31 (2H, m), 3.41-3.48(6H, m), 6.97-7.01 (1H, m), 7.07 (2H, brs), 7.11 (2H, brs), 7.11-7.12 (1H, m), 7.25-7.27 (2H, m), 7.40 (1H, d, J = 7.1 Hz), 8.40 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{19}H_{21}N_5OClS$ 402.1155, found 402.1153;

MS (FAB) m/z: 402 $[M+H]^+$, 246, 189, 182;

Anal. Calcd for $C_{19}H_{20}ClN_5OS \cdot 0.22H_2O$: C, 56.23; H, 5.08; N, 17.25; Cl, 8.73; S, 7.90. Found: C, 56.18; H, 5.11; N, 17.08; Cl, 8.66; S, 7.62.

(Example 62) 3-amino-4-[4-(4-cyanophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-98)

(62a) tert-butyl 4-(4-cyanophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Example 59 (59a) using 4-cyano fluorobenzene (242 mg, 2 mmol) and tert-butoxycarbonyl homopiperazine (801 mg, 4 mmol) and the title compound (364 mg, yield 60%) was obtained.

Brown liquid

IR (film) $\nu_{max}$ 2975, 2214, 1691, 1606, 1521, 1417, 1365, 1240, 1178, 929, 819, 544 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.16 (4.5H, s), 1.28 (4.5H, s), 1.68-1.85 (2H, m), 3.17 (1H, t, J = 5.9 Hz), 3.25 (1H, t, J = 5.5 Hz), 3.44-3.68 (6H, m), 6.81 (2H, d, J = 9.4 Hz), 7.48 (2H, dd, J = 3.5, 9.4 Hz);

HRMS m/z calcd for $C_{17}H_{23}N_3O_2$ 301.1790, found 301.1784;

MS (FAB) m/z: 302 $[M+H]^+$, 301, 246, 228, 200, 120.

(62b) 1-(4-cyanophenyl)-1,4-diazepane

tert-butyl 4-(4-cyanophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 62 (62a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Brown liquid

IR (film) $\nu_{max}$ 2935, 2211, 1606, 1521, 1404, 1178, 817, 544 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.87 (2H, quint, J = 5.9 Hz), 2.81 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.9 Hz), 3.55 (2H, t, J = 5.9 Hz), 3.61 (2H, t, J = 5.9 Hz), 6.65 (2H, t, J = 9.0 Hz), 8.43 (2H, d, J = 9.0 Hz);

HRMS m/z calcd for $C_{12}H_{15}N_3$ 201.1266, found 201.1268;

MS (EI) m/z: 201 $[M^+]$, 171, 159, 145, 131, 116, 102.

(62c) (2Z)-2-cyano-3-[4-(4-cyanophenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(4-cyanophenyl)-1,4-diazepane which was produced in Example 62 (62b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 169-171°C (decomposition);

IR (KBr) $\nu_{max}$ 3290, 2214, 217, 1604, 1519, 1408, 1179, 819, 543 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.88-1.94 (2H, m), 2.21 (3H, s), 3.52 (2H, t, J = 5.5 Hz), 3.58-3.63 (4H, m), 3.82 (2H, t, J = 5.5 Hz), 6.85 (2H, d, J = 9.0 Hz), 7.51 (2H, d, J = 9.0 Hz), 8.38 (1H, brs), 9.02 (1H, brs);

HRMS m/z calcd for $C_{17}H_{20}N_5S$ 326.1440, found 326.1436;

MS (FAB) m/z: 326 $[M+H]^+$, 202, 171, 120.

(62d) (2Z)-2-cyano-3-[4-(4-cyanophenyl)-1,4-diazepan-1-yl]-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide

(2Z)-3-[4-(4-cyanophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 62 (62c) was used in place of (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Yellow powder

Mp 120-126°C;

IR (KBr) $\nu_{max}$ 2926, 2211, 2180, 1606, 1519, 1178, 821, 546 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.94-1.97 (2H, m), 2.44 (3H, s), 2.90 (3H, s) 3.14 (3H, s), 3.64 (2H, t, J = 5.5 Hz), 3.71-3.77(4H, m), 3.90 (2H, t, J = 5.5 Hz), 6.85 (2H, d, J = 9.0 Hz), 7.48 (2H, d, J = 9.0 Hz), 8.41 (1H, s);

HRMS m/z calcd for $C_{20}H_{25}N_6S$ 381.1861, found 381.1856;

MS (FAB) m/z: 381 $[M+H]^+$, 336, 257, 230, 202, 180, 90, 65;

Anal. Calcd for $C_{20}H_{24}N_6S \cdot 0.62H_2O$: C, 61.33; H, 6.50; N, 21.46; S, 8.19. Found: C, 61.36; H, 6.35; N, 21.25, S, 8.11.

(62e) 3-amino-4-[4-(4-cyanophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-[4-(4-cyanophenyl)-1,4-diazepan-1-yl]-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide which was produced in Example 62 (62d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

Yellow powder

Mp 151-153°C;

IR (KBr) $\nu_{max}$ 3439, 3327, 2211, 1605, 1519, 1366, 1178, 938, 818, 544 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.13-2.18 (2H, m), 3.17-3.19 (2H, m), 3.61 (2H, t, J = 6.3 Hz), 3.84 (2H, t, J = 5.1 Hz), 6.86 (2H, d, J = 9.0 Hz), 6.96 (2H, brs), 7.05 (1H, d, J = 5.5 Hz), 7.07 (2H, brs), 7.52 (2H, t, J = 9.0 Hz), 8.37 (1H, d, J = 5.5 Hz);
HRMS m/z calcd for $C_{20}H_{21}N_6OS$ 393.1497, found 393.1501;
MS (FAB) m/z: 393 $[M+H]^+$, 273, 246;
Anal. Calcd for $C_{20}H_{20}N_6OS \cdot 0.94H_2O$: C, 58.67; H, 5.39; N, 20.53. Found: C, 58.99; H, 5.51; N, 20.22.

(Example 63) 3-amino-4-[4-(4-trifluoromethylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-121)

(63a) tert-butyl 4-(4-trifluoromethylphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.
White powder
IR (KBr) $\nu_{max}$ 2974, 1673, 1422, 1332, 1197, 1100, 987, 829 $cm^{-1}$;
$^1$H NMR($CDCl_3$, 400 MHz) δ 1.33 (4.5H, s), 1.41 (4.5H, s), 1.93-1.99 (2H, m), 3.20 (1H, t, J = 6.3 Hz), 3.31 (1H, t, J = 5.9 Hz), 3.54-3.62 (6H, m), 6.67 (2H, d, J = 9.0 Hz), 7.40 (2H, d, J = 9.0 Hz);
HRMS m/z calcd for $C_{17}H_{23}N_2O_2F_3$ 344.1711, found 344.1718;
MS (FAB) m/z: 345 $[M+H]^+$, 344, 289, 243, 214, 174, 120, 57;
Anal. Calcd for $C_{17}H_{23}F_3N_2O_2$: C, 59.29; H, 6.73; N, 8.13. Found: C, 59.38; H, 6.45; N, 7.98.

(63b) 1-(4-trifluoromethylphenyl)-1,4-diazepane

tert-butyl 4-(4-trifluoromethylphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 63 (63a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2936, 1616, 1531, 1402, 1330, 1197, 1106, 818 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.88 (2H, quint, J = 6.3 Hz), 2.81 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.1 Hz), 3.54-3.61 (4H, m), 6.67 (2H, t, J = 9.0 Hz), 8.39 (2H, d, J = 9.0 Hz);

HRMS m/z calcd for $C_{12}H_{15}N_2F_3$ 244.1187, found 244.1182;

MS (EI) m/z: 244 [$M^+$], 225, 214, 202, 188, 174, 159, 145, 69, 43.

(63c) (2Z)-2-cyano-3-[4-(4-trifluoromethylphenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(4-trifluoromethylphenyl)-1,4-diazepane which was produced in Example 63 (63b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 266-269°C (decomposition);

IR (KBr) $\nu_{max}$ 3373, 3267, 3171, 2185, 1614, 1527, 1330, 1104, 822 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.91-1.95 (2H, m), 2.23 (3H, s), 3.51 (2H, t, J = 5.5 Hz), 3.59-3.63 (4H, m), 3.79 (2H, t, J = 5.1 Hz), 6.87 (2H, d, J = 8.6 Hz), 7.42 (2H, d, J = 8.6 Hz), 8.37 (1H, brs), 9.01 (1H, brs);

HRMS m/z calcd for $C_{17}H_{20}N_4F_3S$ 369.1361, found 369.1359;

MS (FAB) m/z: 369 [M+H]$^+$, 335, 245, 227, 200, 166, 63;

Anal. Calcd for $C_{17}H_{19}F_3N_4S \cdot 0.10H_2O$: C, 55.15; H, 5.23; N, 15.13; F, 15.39. Found: C, 54.92; H, 5.26; N, 15.25, F, 15.59.

(63d) (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-trifluoromethylphenyl)-1,4-diazepan-1-yl]but-2-enethioamide

(2Z)-3-[4-(4-trifluoromethylphenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 63 (63c) was used in place of (2Z)-2-

cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Yellow powder

Mp 251-253°C;

IR (KBr) $\nu_{max}$ 2927, 2177, 1614, 1400, 1332, 1201, 1107, 925, 832 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.95-1.99 (2H, m), 2.47 (3H, s), 2.89 (3H, s), 3.12 (3H, s), 3.63 (2H, t, J = 6.3 Hz), 3.70-3.79(4H, m), 3.89 (2H, t, J = 5.1 Hz), 6.90 (2H, d, J = 9.0 Hz), 7.42 (2H, d, J = 9.0 Hz), 8.44 (1H, s);

HRMS m/z calcd for $C_{20}H_{25}N_6F_3S$ 424.1783, found 424.1783;

MS (FAB) m/z: 424 $[M+H]^+$, 390, 379, 352, 245, 227, 200, 188, 90, 73;

Anal. Calcd for $C_{20}H_{24}F_3N_5S$: C, 56.72; H, 5.71; N, 16.54; F, 13.46; S, 7.57. Found: C, 56.46; H, 5.60; N, 16.36, F, 13.32; S, 7.49.

(63e) 3-amino-4-[4-(4-trifluoromethylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-trifluoromethylphenyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 63 (63d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

Pale yellow powder

Mp 204-208°C;

IR (KBr) $\nu_{max}$ 3326, 1614, 1502, 1330, 1199, 1104, 939, 817 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.15-2.19 (2H, m), 3.17-3.22 (2H, m), 3.30-3.32 (2H, m), 3.62 (2H, t, J = 5.5 Hz), 3.84-3.86 (2H, m), 6.91 (2H, d, J = 9.0 Hz), 7.00

(2H, brs), 7.09 (1H, d, J = 5.5 Hz), 7.11 (2H, brs), 7.47 (2H, t, J = 9.0 Hz), 8.41 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{20}H_{21}ON_5F_3S$ 436.1419, found 436.1418;

MS (FAB) m/z: 436 $[M+H]^+$, 419, 246, 214;

Anal. Calcd for $C_{20}H_{20}F_3N_5OS \cdot 0.98H_2O$: C, 53.01; H, 4.88; N, 15.46; F, 12.58; S,7.08. Found: C, 52.79; H, 4.61; N, 15.21; F, 12.97; S, 7.12.

(Example 64) 3-amino-4-{4-[4-(methylthio)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-131)

(64a) tert-butyl 4-[4-(methylthio)phenyl]-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Brown liquid

IR (film) $\nu_{max}$ 2974, 1693, 1595, 1503, 1416, 1365, 1237, 1168, 1125, 930, 810 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.35 (4.5H, s), 1.42 (4.5H, s), 1.91-1.96 (2H, m), 2.39 (3H, s), 3.19 (1H, t, J = 5.9 Hz), 3.30 (1H, t, J = 5.9 Hz), 3.49-3.54 (6H, m), 6.61 (2H, d, J = 8.6 Hz), 7.22 (2H, d, J = 8.6 Hz);

HRMS m/z calcd for $C_{17}H_{26}O_2N_2S$ 322.1715, found 322.1714;

MS (FAB) m/z: 322 $[M^+]$, 266, 221, 178, 57;

Anal. Calcd for $C_{17}H_{26}N_2O_2S \cdot 0.28H_2O$: C, 62.34; H, 8.17; N, 8.55. Found: C, 62.38; H, 8.41; N, 8.38.

(64b) 1-[4-(methylthio)phenyl]-1,4-diazepane

tert-butyl 4-[4-(methylthio)phenyl]-1,4-diazepane-1-carboxylate which was produced in Example 64 (64a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2919, 1595, 1503, 1395, 1195, 809 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.88 (2H, quint, J = 5.9 Hz), 2.40 (3H, s), 2.82 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.1 Hz), 3.47-3.57 (4H, m), 6.64 (2H, d, J = 8.6 Hz), 8.25 (2H, d, J = 8.6 Hz);

HRMS m/z calcd for $C_{12}H_{18}N_2S$ 222.1191, found 222.1178;

MS (EI) m/z: 222 [$M^+$], 192, 180, 166, 151, 137, 108, 91, 77, 70, 56, 43.

(64c) (2Z)-2-cyano-3-{4-[4-(methylthio)phenyl]-1,4-diazepan-1-yl}but-2-enethioamide

1-(4-(methylsulphanylphenyl)-1,4-diazepane which was produced in Example 64 (64b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 159-160°C (decomposition);

IR (KBr) $\nu_{max}$ 3341, 3154, 2178, 1594, 1501, 1392, 1244, 1011, 879, 811 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.90-1.94 (2H, m), 2.23 (3H, s), 2.36 (3H, s), 3.49-3.54 (4H, m), 3.59-3.61 (2H, m), 3.70-3.73 (2H, m), 6.75 (2H, d, J = 8.6 Hz), 7.16 (2H, d, J = 8.6 Hz), 8.35 (1H, brs), 9.01 (1H, brs);

HRMS m/z calcd for $C_{17}H_{22}N_4S_2$ 346.1286, found 346.1245;

MS (EI) m/z: 346 [$M^+$], 272, 247, 222, 205, 192, 178, 166, 151, 137, 123, 96, 68, 59, 42;

Anal. Calcd for $C_{17}H_{22}N_4S_2 \cdot 0.08H_2O$: C, 56.68; H, 6.42; N, 16.10; S, 18.43. Found: C, 58.47; H, 6.32; N, 15.98, S, 18.39.

(64d) (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-{4-[4-(methylthio)phenyl]-1,4-diazepan-1-yl}but-2-enethioamide

(2Z)-3-{4-[4-(methylthio)phenyl]-1,4-diazepan-1-yl}-2-cyanobut-2-enethioamide which was produced in Example 64 (64c) was used in place of (2Z)-2-

cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Yellow powder

Mp 133-136°C;

IR (KBr) $\nu_{max}$ 2921, 2177, 1610, 1501, 1396, 1325, 1291, 1195, 1011, 923, 815 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.93-1.98 (2H, m), 2.35 (3H, s), 2.49 (3H, s), 2.92 (3H, s), 3.14 (3H, s), 3.53 (2H, t, J = 5.9 Hz), 3.69-3.81 (6H, m), 6.75 (2H, d, J = 9.0 Hz), 7.14 (2H, d, J = 9.0 Hz), 8.46 (1H, s);

HRMS m/z calcd for $C_{20}H_{28}N_5S_2$ 402.1786, found 402.1770;

MS (FAB) m/z: 402 $[M+H]^+$, 368, 330, 221, 192, 178, 166;

Anal. Calcd for $C_{20}H_{27}N_5S_2 \cdot 0.2H_2O$: C, 59.28; H, 6.82; N, 17.28; S, 15.83. Found: C, 59.53; H, 6.80; N, 17.00; S, 15.96.

(64e) 3-amino-4-{4-[4-(methylthio)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-{4-[4-(methylthio)phenyl]-1,4-diazepan-1-yl}but-2-enethioamide which was produced in Example 64 (64d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in 58 embodiment (58e) and the title compound was obtained.

Pale yellow powder

Mp 186-188°C;

IR (KBr) $\nu_{max}$ 3433, 3326, 3163, 1657, 1592, 1500, 1367, 1232, 940, 811 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.09-2.14 (2H, m), 2.36 (3H, s), 3.16-3.18 (2H, m), 3.25-3.28 (2H, m), 3.52 (2H, t, J = 6.3 Hz), 3.74 (2H, t, J = 4.7 Hz), 6.73 (2H, d, J =

9.0 Hz), 6.94 (2H, brs), 7.05 (1H, d, J = 5.1 Hz), 7.06 (2H, brs), 7.17 (2H, t, J = 9.0 Hz), 8.37 (1H, d, J = 5.1 Hz);

HRMS m/z calcd for $C_{20}H_{24}ON_5S_2$ 414.1422, found 414.1414;

MS (FAB) m/z: 414 $[M+H]^+$, 413, 397, 275, 230, 218, 192, 178, 166;

Anal. Calcd for $C_{20}H_{23}N_5OS_2$: C, 58.08; H, 5.61; N, 16.93; S, 15.51. Found: C, 57.91; H, 5.66; N, 16.68; S, 15.42.

(Example 65) 3-amino-4-[4-(3-toluyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-110)

(65a) tert-butyl 4-(3-toluyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

Brown liquid

IR (film) $\nu_{max}$ 2974, 1695, 1602, 1498, 1415, 1175, 930, 692 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.36 (4.5H, s), 1.44 (4.5H, s), 1.92-1.98 (2H, m), 2.28 (3H, s), 3.19 (1H, t, J = 6.3 Hz), 3.29 (1H, t, J = 6.3 Hz), 3.49-3.54 (6H, m), 6.46-6.48 (3H, m), 7.06 (1H, t, J = 7.1 Hz);

HRMS m/z calcd for $C_{17}H_{26}O_2N_2$ 290.1994, found 290.1981;

MS (FAB) m/z: 290 $[M^+]$, 235, 217, 189, 120, 91, 70, 57;

Anal. Calcd for $C_{17}H_{26}N_2O_2 \cdot 0.16H2O$: C, 69.62; H, 9.05; N, 9.55. Found: C, 69.71; H, 9.36; N, 9.28.

(65b) 1-(3-toluyl)-1,4-diazepane

tert-butyl 4-(3-toluyl)-1,4-diazepane-1-carboxylate which was produced in Example 65 (65a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2928, 1601, 1498, 1363, 1178, 765, 692 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.88 (2H, quint, J = 4.3 Hz), 2.29 (3H, s), 2.82 (2H, t, J = 5.9 Hz), 3.02 (2H, t, J = 5.1 Hz), 3.52-3.57 (4H, m), 6.47-6.51 (3H, m), 7.09 (2H, dd, J = 1.9, 9.4 Hz);

HRMS m/z calcd for $C_{12}H_{18}N_2$ 190.1470, found 190.1456;

MS (EI) m/z: 190 [$M^+$], 160, 148, 134, 122, 105, 91, 77, 65, 43.

(65c) (2Z)-2-cyano-3-[4-(3-toluyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(3-toluyl)-1,4-diazepane which was produced in Example 65 (65b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 144-148°C;

IR (KBr) $\nu_{max}$ 3151, 2188, 1601, 1542, 1345, 1174, 912, 766 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.91-1.95 (2H, m), 2.22 (3H, s), 2.23 (3H, s), 3.48-3.54 (4H, m), 3.60-3.63 (2H, m), 3.68-3.71 (2H, m), 6.44 (1H, d, J = 7.0 Hz), 6.55-6.57 (2H, m), 7.03 (1H, t, J = 7.0 Hz), 8.34 (1H, brs), 9.01 (1H, brs);

HRMS m/z calcd for $C_{17}H_{23}N_4S$ 315.1644, found 315.1645;

MS (FAB) m/z: 315 $[M+H]^+$, 281, 256, 246, 173;

Anal. Calcd for $C_{17}H_{22}N_4S$: C, 64.93; H, 7.05; N, 17.82; S, 10.20. Found: C, 64.65; H, 7.05; N, 17.73, S, 10.13.

(65d) (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(3-toluyl)-1,4-diazepan-1-yl]but-2-enethioamide

(2Z)-3-[4-(3-toluyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 65 (65c) was used in place of (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Yellow powder

Mp 256-260°C (decomposition);

IR (KBr) $\nu_{max}$ 2178, 1608, 1394, 1292, 1181, 1118, 773, 692 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.94-1.99 (2H, m), 2.21 (3H, s), 2.49 (3H, s), 2.92 (3H, s), 3.14 (3H, s), 3.54 (2H, t, J = 5.9 Hz), 3.68-3.77(6H, m), 6.43 (1H, d, J = 7.8 Hz), 6.55-6.58 (2H, m), 7.02 (1H, t, J = 7.8 Hz), 8.45 (1H, s);

HRMS m/z calcd for $C_{20}H_{28}N_5S$ 370.2065, found 370.2057;

MS (FAB) m/z: 370 $[M+H]^+$, 354, 336, 325, 298, 281, 235, 208, 196, 180, 173, 160, 134, 115, 90, 58;

Anal. Calcd for $C_{20}H_{27}N_5S \cdot 0.06H_2O$: C, 64.82; H, 7.38; N, 18.90; S, 8.65. Found: C, 64.85; H, 7.22; N, 18.61; S, 8.95.

(65e) 3-amino-4-[4-(3-toluyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(3-toluyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 65 (65d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

Pale yellow powder

Mp 209-212°C;

IR (KBr) $\nu_{max}$ 3327, 3169, 2830, 1637, 1579, 1498, 1373, 1234, 1182, 942, 767 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.10-2.15 (2H, m), 2.22 (3H, s), 3.14-3.18 (2H, m), 3.26-3.28 (2H, m), 3.52 (2H, t, J = 6.3 Hz), 3.73 (2H, t, J = 4.7 Hz), 6.41 (1H, d, J = 7.8 Hz), 6.53-6.56 (2H, m), 6.97 (2H, brs), 7.01 (1H, t, J = 7.8 Hz), 7.05 (1H, d, J = 5.5 Hz), 7.06 (2H, brs), 8.37 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{20}H_{24}ON_5S$ 382.1702, found 382.1699;

MS (FAB) m/z: 382 $[M+H]^+$, 365, 248, 230, 218, 202, 176;

Anal. Calcd for $C_{20}H_{23}N_5OS \cdot 0.08H_2O$: C, 62.73; H, 6.10; N, 18.29; S, 8.37. Found: C, 62.56; H, 6.08; N, 18.14; S, 8.32.

(Example 66) 3-amino-4-{4-[4-(methylsulfinyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-132)

3-amino-4-{4-[4-(methylthio)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (57 mg, 0.14 mmol) which was produced in Example 64 (64e) was dissolved in methanol (5 mL), and was blended with an aqueous solution (1 mL) of sodium periodate (33 mg, 0.15 mmol) and heated under reflux for one hour. Water (10 mL) was added to the reaction liquid and after stirring for two hours, generated powder was separated by filtration and the title compound (53 mg, yield 89%) was obtained.

White powder

Mp 153-157°C;

IR (KBr) $\nu_{max}$ 3439, 3324, 3182, 1646, 1592, 1505, 1367, 1093, 1037, 939, 814 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.13-2.17 (2H, m), 2.67 (3H, s), 3.18-3.22 (2H, m), 3.29-3.31 (2H, m), 3.61 (2H, t, J = 6.3 Hz), 3.84 (2H, t, J = 6.3 Hz), 6.93 (2H, d, J = 9.0 Hz), 6.94 (2H, brs), 7.09 (1H, d, J = 5.1 Hz), 7.09 (2H, brs), 7.49 (2H, t, J = 9.0 Hz), 8.40 (1H, d, J = 5.1 Hz);

HRMS m/z calcd for $C_{20}H_{24}O_2N_5S_2$ 430.1371, found 430.1386;

MS (FAB) m/z: 430 $[M+H]^+$, 412, 395, 242, 230, 204, 166, 65;

Anal. Calcd for $C_{20}H_{23}N_5O_2S_2 \cdot 2.1H_2O$: C, 51.40; H, 5.87; N, 14.98; S, 13.72. Found: C, 51.61; H, 5.87; N, 15.00; S, 13.52.

(Example 67) 3-amino-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-122)

(67a) tert-butyl 4-(2-methoxyphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

Brown liquid

IR (film) $\nu_{max}$ 2975, 1694, 1503, 1415, 1242, 1165, 1029, 745 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.14-1.46 (9H, m), 1.89-2.00 (2H, m), 3.18-3.31 (4H, m), 3.48-3.62 (4H, m), 3.83 (3H, s), 6.81-6.93 (4H, m);

HRMS m/z calcd for $C_{17}H_{26}O_3N_2$ 306.1943, found 306.1972;

MS (EI) m/z: 306 [$M^+$], 249, 233, 205, 188, 176, 162, 150, 134, 120, 57.

(67b) 1-(2-methoxyphenyl)-1,4-diazepane

tert-butyl 4-(2-methoxyphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 67 (67a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2938, 1593, 1502, 1242, 1028, 744 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.96 (2H, quint, J = 5.9 Hz), 3.05 (2H, t, J = 5.5 Hz), 3.11 (2H, t, J = 5.5 Hz), 3.30-3.34 (4H, m), 3.84 (3H, s), 6.83-6.96 (4H, m);

HRMS m/z calcd for $C_{12}H_{18}ON_2$ 206.1419, found 206.1417;

MS (EI) m/z: 206 [$M^+$], 176, 164, 150, 136, 120, 109, 91, 77, 43.

(67c) (2Z)-2-cyano-3-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(2-methoxyphenyl)-1,4-diazepane which was produced in Example 67 (67b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Yellow amorphous

IR (KBr) $\nu_{max}$ 3287, 3171, 2918, 2184, 1607, 1533, 1452, 1238, 1024, 751 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.93-1.98 (2H, m), 2.33 (3H, s), 3.14-3.17 (2H, m), 3.25-3.37 (2H, m), 3.60-3.66 (4H, m), 3.75 (3H, s), 6.79-6.90 (4H, m), 8.23 (1H, brs), 8.91 (1H, brs);

HRMS m/z calcd for $C_{17}H_{23}ON_4S$ 331.1593, found 331.1587;

MS (FAB) m/z: 331 $[M+H]^+$, 315, 273, 200, 165, 63.

(67d) 3-amino-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 67 (67c) was used in place of (2Z)-3-[4-(2-chlorophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide and the reaction was performed in a similar method as described in Example 61 (61d) and the title compound was obtained.

Pale yellow powder

Mp 179-184°C;

IR (KBr) $\nu_{max}$ 3440, 3314, 3141, 1581, 1500, 1371, 1235, 937, 751 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.04-2.10 (2H, m), 3.25-3.40 (8H, m), 3.75 (3H, s), 6.80-6.93 (4H, m), 7.05 (2H, brs), 7.08 (2H, brs), 7.11 (1H, d, J = 5.5 Hz), 8.39 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{20}H_{24}O_2N_5S$ 398.1651, found 398.1653;

MS (FAB) m/z: 398 $[M+H]^+$, 273, 246, 200, 63;

Anal. Calcd for $C_{20}H_{23}N_5O_2S \cdot 0.14H_2O$: C, 60.05; H, 5.87; N, 17.51; S, 8.02. Found: C, 59.87; H, 5.87; N, 17.43; S, 7.85.

(Example 68) 3-amino-4-[4-(3-methoxyphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-123)

(68a) tert-butyl 4-(3-methoxyphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Brown liquid

IR (film) $\nu_{max}$ 2973, 1694, 1612, 1500, 1416, 1165, 930, 753 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.37 (4.5H, s), 1.44 (4.5H, s), 1.93-2.00 (2H, m), 3.19 (1H, t, J = 6.3 Hz), 3.28-3.30 (1H, m), 3.49-3.55 (6H, m), 3.77 (3H, s), 6.23-6.25 (2H, m), 6.32 (1H, d, J = 7.0 Hz), 7.11 (1H, t, J = 7.0 Hz);

HRMS m/z calcd for $C_{17}H_{26}O_3N_2$ 306.1943, found 306.1937;

MS (EI) m/z: 306 [$M^+$], 250, 235, 205, 188, 176, 162, 150, 121, 70, 57;

Anal. Calcd for $C_{17}H_{26}N_2O_3 \cdot 0.38H2O$: C, 65.18; H, 8.61; N, 8.94. Found: C, 65.22; H, 8.59; N, 8.79.

(68b) 1-(3-methoxyphenyl)-1,4-diazepane

tert-butyl 4-(3-methoxyphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 68 (68a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2935, 1611, 1500, 1166, 1054, 923, 752, 688 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.88 (2H, quint, J = 5.9 Hz), 2.82 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.9 Hz), 3.51-3.57 (4H, m), 3.78 (3H, s), 6.21-6.24 (2H, m), 6.32 (1H, dd, J = 1.9, 9.4 Hz), 7.11 (1H, t, J = 9.4 Hz);

HRMS m/z calcd for $C_{12}H_{18}ON_2$ 206.1420, found 206.1403;

MS (EI) m/z: 206 [$M^+$], 164, 150, 138, 121, 70, 56.

(68c) (2Z)-2-cyano-3-[4-(3-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(3-methoxyphenyl)-1,4-diazepane which was produced in Example 68 (68b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 129-131°C;

IR (KBr) $\nu_{max}$ 3349, 3154, 2939, 2187, 1611, 1541, 1344, 1167, 1058, 914, 749 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.91-1.94 (2H, m), 2.23 (3H, s), 3.49-3.54 (4H, m), 3.59-3.62 (2H, m), 3.69 (3H, s), 3.69-3.73 (2H, m), 6.21 (1H, d, J = 9.0 Hz), 6.25 (1H, s), 6.35 (1H, d, J = 9.0 Hz), 7.05 (1H, t, J = 9.0 Hz), 8.35 (1H, brs), 9.02 (1H, brs);

HRMS m/z calcd for $C_{17}H_{23}ON_4S$ 331.1592, found 331.1575;

MS (FAB) m/z: 331 $[M+H]^+$, 246, 200, 165, 63;

Anal. Calcd for $C_{17}H_{22}N_4OS$: C, 61.79; H, 6.71; N, 16.95; S, 9.70. Found: C, 61.72; H, 6.66; N, 16.85, S, 9.44.

(68d) 4-[4-(3-methoxyphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-[4-(3-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide (476 mg, 1.44 mmol) which was produced in Example 68 (68c) and N,N-dimethylformamide dimethylacetal (344 mg, 2.88 mmol) were mixed with ethanol (15 mL) and the mixture was stirred at room temperature for 18 hours. The crystal which was deposited was separated by filtration and the title compound was obtained 490 mg (yield 27%).

Pale yellow powder

Mp 224-227°C (decomposition);

IR (KBr) $\nu_{max}$ 2955, 2208, 1608, 1499, 1256, 1166, 1052, 929, 756, 687 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.90-1.95 (2H, m), 3.51 (2H, t, J = 5.4 Hz), 3.69 (3H, s), 3.71-3.73 (4H, m), 3.95 (2H, t, J = 5.4 Hz), 6.20 (1H, d, J = 7.8 Hz), 6.26 (1H, s), 6.37 (1H, t, J = 7.8 Hz), 6.43 (1H, d, J = 7.8 Hz), 7.05 (1H, t, J = 7.8 Hz), 7.37 (1H, d, J = 7.8 Hz), 12.51 (1H, brs);

HRMS m/z calcd for $C_{18}H_{21}ON_4S$ 341.1436, found 341.1445;

MS (FAB) m/z: 341 $[M+H]^+$, 273, 246, 200, 165, 63;

Anal. Calcd for $C_{18}H_{20}N_4OS \cdot 0.12H_2O$: C, 63.10; H, 5.95; N, 16.35; S, 9.36. Found: C, 62.84; H, 5.97; N, 16.35, S, 9.36.

(68e) 3-amino-4-[4-(3-methoxyphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(3-methoxyphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 68 (68d) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Pale yellow powder

Mp 193-195°C;

IR (KBr) $\nu_{max}$ 3426, 3319, 3145, 1611, 1499, 1372, 1228, 1167, 1054, 943, 822 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.11-2.16 (2H, m), 3.16-3.21 (2H, m), 3.26-3.30 (2H, m), 3.53 (2H, t, J = 6.7 Hz), 3.70 (3H, s), 3.75 (2H, t, J = 4.7 Hz), 6.22 (1H, dd, J = 2.4, 8.2 Hz), 6.26 (1H, t, J = 2.4 Hz), 6.37 (1H, dd, J = 2.4, 8.2 Hz), 7.00 (2H, brs), 7.04-7.08 (2H, m), 7.09 (2H, brs), 8.40 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{20}H_{24}O_2N_5S$ 398.1651, found 398.1639;

MS (FAB) m/z: 398 $[M+H]^+$, 273, 246, 200, 63;

Anal. Calcd for $C_{20}H_{23}N_5O_2S \cdot 0.16H_2O$: C, 60.00; H, 5.87; N, 17.49; S, 8.01. Found: C, 59.86; H, 5.67; N, 17.29; S, 7.83.

(Example 69) 3-amino-4-[4-(4-fluoro-3-methylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-118)

(69a) tert-butyl 4-(4-fluoro-3-methylphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Brown liquid

IR (film) $\nu_{max}$ 2975, 1694, 1509, 1416, 1366, 1232, 1170, 931, 762 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.34 (4.5H, s), 1.42 (4.5H, s), 1.91-1.95 (2H, m), 2.20 (3H, s), 3.18 (1H, t, J = 5.9 Hz), 3.29 (1H, t, J = 5.9 Hz), 3.44-3.55 (6H, m), 6.37-6.44 (2H, m), 6.81 (1H, t, J = 8.6 Hz);

HRMS m/z calcd for $C_{17}H_{25}O_2N_2F$ 308.1900, found 308.1892;

MS (EI) m/z: 308 [$M^+$], 253, 251, 207, 205, 164, 152, 138, 123, 109, 57;

Anal. Calcd for $C_{17}H_{25}FN_2O_2$: C, 66.21; H, 8.17; N, 9.08; F, 6.16. Found: C, 66.50; H, 7.29; N, 8.88; F, 6.18.

(69b) 1-(4-fluoro-3-methylphenyl)-1,4-diazepane

tert-butyl 4-(4-fluoro-3-methylphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 69 (69a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2929, 1615, 1509, 1228, 839, 797, 761 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.88 (2H, quint, J = 6.3 Hz), 2.23 (3H, s), 2.83 (2H, t, J = 5.9 Hz), 3.02 (2H, t, J = 5.5 Hz), 3.48-3.54 (4H, m), 6.42-6.48 (2H, m), 6.85 (1H, t, J = 9.0 Hz);

HRMS m/z calcd for $C_{12}H_{17}N_2F$ 208.1575, found 208.1353;

MS (EI) m/z: 208 [$M^+$], 178, 166, 152, 138, 123, 109, 43;

(69c) (2Z)-2-cyano-3-[4-(4-fluoro-3-methylphenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(4-fluoro-3-methylphenyl)-1,4-diazepane which was produced in Example 69 (69b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 146-150°C (decomposition);

IR (KBr) $\nu_{max}$ 3328, 3152, 2189, 1627, 1543, 1508, 1389, 1220, 1056, 917, 868, 801 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.88-1.96 (2H, m), 2.18 (3H, s), 2.24 (3H, s), 3.48-3.53 (4H, m), 3.60-3.62 (2H, m), 3.66-3.69 (2H, m), 6.54-6.60 (1H, m), 6.64-6.67 (1H, m), 6.92 (1H, t, J = 9.0 Hz), 8.35 (1H, brs), 9.01 (1H, brs);

HRMS m/z calcd for $C_{17}H_{22}N_4FS$ 333.1536, found 333.1534;

MS (FAB) m/z: 333 $[M+H]^+$, 299, 274, 207, 191, 178, 164, 123, 65, 51;

Anal. Calcd for $C_{17}H_{21}FN_4S$: C, 61.42; H, 6.37; N, 16.85; S, 9.65. Found: C, 61.18; H, 6.29; N, 16.71, S, 9.74.

(69d) (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-fluoro-3-methylphenyl)-1,4-diazepan-1-yl]but-2-enethioamide

(2Z)-3-[4-(4-fluoro-3-methylphenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 69 (69c) was used in place of (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Yellow powder

Mp 148-150°C;

IR (KBr) $\nu_{max}$ 2923, 2178, 1609, 1509, 1324, 1292, 1118, 1015, 512 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.94-1.99 (2H, m), 2.15 (3H, s), 2.47 (3H, s), 2.92 (3H, s), 3.14 (3H, s), 3.51 (2H, t, J = 5.9 Hz), 3.72 (2H, t, J = 5.4 Hz), 3.73-3.77 (4H, m), 6.55-6.59 (1H, m), 6.64-6.66 (1H, m), 6.80 (1H, t, J = 9.3 Hz), 8.45 (1H, s);

HRMS m/z calcd for $C_{20}H_{27}N_5FS$ 388.1971, found 388.1962;

MS (FAB) m/z: 388 $[M+H]^+$, 354, 299, 273, 165, 120, 65, 51;

Anal. Calcd for $C_{20}H_{26}FN_5S$: C, 61.99; H, 6.76; N, 18.07; F, 4.90; S, 8.27. Found: C, 61.75; H, 6.57; N, 17.81; F, 4.77; S, 8.31.

(69e) 3-amino-4-[4-(4-fluoro-3-methylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-fluoro-3-methylphenyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 69 (69d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

White powder

Mp 194-197°C;

IR (KBr) $\nu_{max}$ 3414, 3326, 3172, 1637, 1579, 1507, 1374, 1209, 943 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.10-2.18 (2H, m), 2.18 (3H, s), 3.15-3.21 (2H, m), 3.27-3.29 (2H, m), 3.50 (2H, t, J = 6.3 Hz), 3.71 (2H, t, J = 4,7 Hz), 6.52-6.56 (1H, m), 6.62-6.64 (1H, m), 6.91 (1H, t, J = 9.0 Hz), 6.98 (2H, brs), 7.06 (1H, d, J = 5.5 Hz), 7.07 (2H, brs), 8.38 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{20}H_{23}ON_5FS$ 400.1607, found 400.1632;

MS (FAB) m/z: 400 $[M+H]^+$, 383, 275, 236, 209;

Anal. Calcd for $C_{20}H_{22}FN_5OS \cdot 0.14H_2O$: C, 59.75; H, 5.59; N, 17.42; F, 4.73; S, 7.98. Found: C, 59.82; H, 5.58; N, 17.42; F, 4.45; S, 7.71.

(Example 70) 3-amino-4-[4-(2-toluyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-109)

(70a) tert-butyl 4-(2-toluyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in J. Org. Chem. 68, 452-459 (2003) and the title compound was synthesized.

Brown liquid

IR (film) $\nu_{max}$ 2975, 1695, 1492, 1413, 1159, 762, 725 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.47-1.48 (9H, m), 1.87-1.97 (2H, m), 2.29 (3H, s), 3.00-3.10 (4H, m), 3.52-3.60 (4H, m), 6.92 (1H, t, J = 7.8 Hz), 7.01 (1H, d, J = 7.8 Hz), 7.08-7.14 (2H, m);

HRMS m/z calcd for $C_{17}H_{26}O_2N_2$ 290.1994, found 290.1977;

MS (FAB) m/z: 290 [$M^+$], 249, 233, 189, 166, 146, 130, 95, 51.

(70b) 1-(2-toluyl)-1,4-diazepane

tert-butyl 4-(2-toluyl)-1,4-diazepane-1-carboxylate which was produced in Example 70 (70a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2938, 2831, 1598, 1492, 1458, 1213, 1163, 1114, 759, 724 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.89 (2H, quint, J = 5.9 Hz), 2.32 (3H, s), 3.02 (2H, t, J = 4.3 Hz), 3.07 (2H, t, J = 5.9 Hz), 3.12-3.17 (4H, m), 6.94 (1H, t, J = 7.8 Hz), 7.07 (1H, d, J = 7.8 Hz), 7.12-7.17 (2H, m);

HRMS m/z calcd for $C_{12}H_{18}N_2$ 190.1470, found 190.1443;

MS (EI) m/z: 190 [$M^+$], 160, 148, 134, 118, 105, 91, 77, 65, 43.

(70c) (2Z)-2-cyano-3-[4-(2-toluyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(2-toluyl)-1,4-diazepane which was produced in Example 70 (70b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 99-100°C;

IR (KBr) $\nu_{max}$ 3286, 3173, 2184, 1599, 1521, 1410, 1294, 1220, 881, 765 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 2.00-2.04 (2H, m), 2.24 (3H, s), 2.36 (3H, s), 3.01 (2H, t, J = 5.4 Hz), 3.16-3.17 (2H, m), 3.66 (2H, t, J = 5.4 Hz), 3.70-3.72 (2H, m), 6.95 (1H, t, J = 6.8 Hz), 7.07 (1H, d, J = 7.3 Hz), 7.12-7.17 (2H, m), 8.27 (1H, brs), 8.93 (1H, brs);

HRMS m/z calcd for $C_{17}H_{23}N_4S$ 315.1644, found 315.1643;

MS (FAB) m/z: 315 $[M+H]^+$, 281, 256, 189, 173, 65, 39;

Anal. Calcd for $C_{17}H_{22}N_4S \cdot 0.56H_2O$: C, 62.92; H, 7.18; N, 17.26; S, 9.88. Found: C, 62.65; H, 6.88; N, 17.11, S, 9.13.

(70d) 3-amino-4-[4-(2-toluyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-[4-(2-toluyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 70 (70c) was used in place of (2Z)-3-[4-(2-chlorophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide and the reaction was performed in a similar method as described in Example 61 (61d) and the title compound was obtained.

Pale yellow powder

Mp 206-209°C (decomposition);

IR (KBr) $\nu_{max}$ 3427, 3308, 3142, 1583, 1493, 1374, 1228, 1053, 944, 767 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.97-2.04 (2H, m), 2.23 (3H, s), 3.11 (2H, t, J = 5.9 Hz), 3.22-3.25 (2H, m), 3.38-3.42 (2H, m), 6.84-6.88 (1H, m), 7.00-7.10 (7H, m), 8.34 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{20}H_{24}ON_5S$ 382.1702, found 382.1701;

MS (FAB) m/z: 382 $[M+H]^+$, 246, 185, 107;

Anal. Calcd for $C_{20}H_{23}N_5OS$: C, 62.97; H, 6.08; N, 18.36. Found: C, 62.79; H, 6.27; N, 18.20.

(Example 71) 3-amino-4-[4-(3-fluoro-4-methylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-117)

(71a) tert-butyl 4-(3-fluoro-4-methylphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Brown liquid

IR (film) $\nu_{max}$ 2975, 1695, 1634, 1518, 1416, 1366, 1246, 1171, 1124, 930 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.38 (4.5H, s), 1.45 (4.5H, s), 1.93-1.99 (2H, m), 2.14 (3H, s), 3.20 (1H, t, J = 5.9 Hz), 3.30 (1H, t, J = 5.9 Hz), 3.45-3.55 (6H, m), 6.33-6.36 (2H, m), 6.96 (1H, t, J = 8.6 Hz);

HRMS m/z calcd for $C_{17}H_{25}O_2N_2F$ 308.1900, found 308.1877;

MS (EI) m/z: 308 [$M^+$], 253, 207, 178, 164, 152, 138, 123, 109, 57.

(71b) 1-(3-fluoro-4-methylphenyl)-1,4-diazepane

tert-butyl 4-(3-fluoro-4-methylphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 71 (71a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2929, 1634, 1518, 1459, 1119, 927, 822 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.88 (2H, quint, J = 5.9 Hz), 2.14 (3H, s), 2.82 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.9 Hz), 3.50 (2H, t, J = 5.9 Hz), 5.53 (2H, t, J = 5.9 Hz), 6.34-6.38 (2H, m), 6.97 (1H, t, J = 9.0 Hz);

HRMS m/z calcd for $C_{12}H_{17}N_2F$ 208.1576, found 208.1360;

MS (EI) m/z: 208 [$M^+$], 178, 166, 152, 138, 123, 109, 44.

(71c) (2Z)-2-cyano-3-[4-(3-fluoro-4-methylphenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(3-fluoro-4-methylphenyl)-1,4-diazepane which was produced in Example 71 (71b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Yellow powder

Mp 155-157°C (decomposition);

IR (KBr) $\nu_{max}$ 3163, 2184, 1632, 1516, 1350, 1173, 1120, 872 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.90-1.94 (2H, m), 2.08 (3H, s), 2.25 (3H, s), 3.51-3.53 (4H, m), 3.59-3.61 (2H, m), 3.70-3.72 (2H, m), 6.50 (1H, dd, J = 2.4, 8.8 Hz), 6.56 (1H, dd, J = 2.4, 13.8 Hz), 7.02 (1H, t, J = 8.8 Hz), 8.35 (1H, brs), 9.01 (1H, brs);

HRMS m/z calcd for $C_{17}H_{21}N_4FSNa$ 355.1369, found 355.1354;

MS (ESI) m/z: 355.14 $[M+Na]^+$;

Anal. Calcd for $C_{17}H_{21}FN_4S$: C, 61.42; H, 6.37; N, 16.85; F, 5.71. Found: C, 61.07; H, 6.21; N, 16.66, F, 6.06.

(71d) (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(3-fluoro-4-methylphenyl)-1,4-diazepan-1-yl]but-2-enethioamide

(2Z)-3-[4-(3-fluoro-4-methylphenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 71 (71c) was used in place of (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Yellow powder

Mp 254-256°C;

IR (KBr) $\nu_{max}$ 2925, 2177, 1608, 1517, 1397, 1291, 1120, 1013, 906, 512 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.94-1.98 (2H, m), 2.07 (3H, s), 2.49 (3H, s), 2.93 (3H, s), 3.15 (3H, s), 3.53 (2H, t, J = 5.9 Hz), 3.71 (2H, t, J = 5.4 Hz), 3.77-3.81 (4H,

m), 6.51 (1H, dd, J = 2.4, 8.3 Hz), 6.56 (1H, dd, J = 2.4, 13.7 Hz), 7.01 (1H, t, J = 8.3 Hz), 8.46 (1H, s);

HRMS m/z calcd for $C_{20}H_{27}N_5FS$ 388.1971, found 388.1986;

MS (FAB) m/z: 388 $[M+H]^+$, 354, 273, 242, 209, 166;

Anal. Calcd for $C_{20}H_{26}FN_5S$: C, 61.99; H, 6.76; N, 18.07; F, 4.90; S, 8.27. Found: C, 61.73; H, 6.87; N, 18.08; F, 4.92; S, 8.29.

(71e) 3-amino-4-[4-(3-fluoro-4-methylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(3-fluoro-4-methylphenyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 71 (71d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

Pale yellow powder

Mp 79-83°C;

IR (KBr) $\nu_{max}$ 3440, 3323, 3177, 2926, 1633, 1578, 1517, 1368, 1118, 943, 824 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.07-2.15 (2H, m), 2.09 (3H, s), 3.15-3.20 (2H, m), 3.23-3.27 (2H, m), 3.51 (2H, t, J = 6.3 Hz), 3.73 (2H, t, J = 4,7 Hz), 6.47-6.54 (2H, m), 6.97 (2H, brs), 7.02 (1H, t, J = 8.7 Hz), 7.06 (1H, d, J = 5.5 Hz), 7.08 (2H, brs), 8.38 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{20}H_{23}ON_5FS$ 400.1608, found 400.1559;

MS (FAB) m/z: 400 $[M+H]^+$, 278, 246, 185, 83, 57;

Anal. Calcd for $C_{20}H_{22}FN_5OS \cdot 0.56H_2O$: C, 58.65; H, 5.69; N, 17.10; F, 4.64. Found: C, 58.93; H, 6.04; N, 17.04; F, 4.89.

(Example 72) 3-amino-4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-88)

(72a) tert-butyl 4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

Brown liquid

IR (film) $\nu_{max}$ 2974, 1692, 1511, 1416, 1284, 1170, 1072, 931 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.39 (4.5H, s), 1.45 (4.5H, s), 1.92-1.99 (2H, m), 3.20 (1H, t, J = 6.3 Hz), 3.30 (1H, t, J = 5.9 Hz), 3.43-3.49 (4H, m), 3.53-3.55 (2H, m), 4.17-4.18 (2H, m), 4.22-4.23 (2H, m), 6.18-6.22 (2H, m), 6.72 (1H, d, J = 9.8 Hz);

HRMS m/z calcd for $C_{18}H_{27}O_4N_2$ 335.1971, found 335.1974;

MS (FAB) m/z: 334 [$M^+$], 278, 246, 235, 189, 145, 139, 83, 57;

Anal. Calcd for $C_{18}H_{26}N_3O_4 \cdot 0.26H_2O$: C, 63.76; H, 7.88; N, 8.27. Found: C, 63.75; H, 7.66; N, 8.02.

(72b) 1-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,4-diazepane

tert-butyl 4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,4-diazepane-1-carboxylate which was produced in Example 72 (72a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2929, 1626, 1510, 1284, 1071, 822, 789 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.87 (2H, quint, J = 6.3 Hz), 2.82 (2H, t, J = 5.9 Hz), 3.00 (2H, t, J = 5.5 Hz), 3.45-3.50 (4H, m), 4.17-4.19 (2H, m), 4.22-4.24 (2H, m), 6.19-6.22 (2H, m), 6.72 (1H, d, J = 9.4 Hz);

HRMS m/z calcd for $C_{13}H_{18}O_2N_2$ 234.1368, found 234.1373;

MS (EI) m/z: 234 [$M^+$], 204, 192, 178, 166, 149, 136, 117, 79, 56, 43.

(72c) (2Z)-2-cyano-3-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,4-diazepane which was produced in Example 72 (72b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Yellow powder

Mp 114-116°C;

IR (KBr) $\nu_{max}$ 3314, 3155, 2185, 1542, 1510, 1286, 1211, 1068, 869 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.88-1.84 (2H, m), 2.25 (3H, s), 3.40-3.45 (2H, m), 3.46-3.52 (2H, m), 3.59 (4H, brs), 4.10-4.12 (2H, m), 4.16-4.18 (2H, m), 6.24-6.27 (2H, m), 6.65 (1H, d, J = 9.5 Hz), 8.30 (1H, brs), 8.97 (1H, brs);

HRMS m/z calcd for $C_{18}H_{23}O_2N_4S$ 359.1542, found 359.1540;

MS (FAB) m/z: 359 $[M+H]^+$, 338, 273, 226, 182, 165, 120, 63;

Anal. Calcd for $C_{18}H_{22}N_4O_2S$: C, 59.30; H, 6.27; N, 15.37. Found: C, 59.04; H, 6.18; N, 15.71.

(72d) (2Z)-2-cyano-3-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,4-diazepan-1-yl]-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide

(2Z)-2-cyano-3-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 72 (72c) was used in place of (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Yellow powder

Mp 127-129°C;

IR (KBr) $\nu_{max}$ 3429, 2925, 2179, 1610, 1410, 1293, 1209, 1069, 513 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.92-1.98 (2H, m), 2.50 (3H, s), 2.95 (3H, s), 3.15 (3H, s), 3.45 (2H, t, J = 5.9 Hz), 3.67-3.72 (4H, m), 3.75-3.77 (2H, m), 4.11-4.13 (2H, m), 4.16-4.18 (2H, m), 6.26-6.29 (2H, m), 6.66 (1H, d, J = 9.4 Hz), 8.48 (1H, s);

HRMS m/z calcd for $C_{21}H_{28}O_2N_5S$ 414.1964, found 414.1974;

MS (FAB) m/z: 413 $[M+H]^+$, 380, 342, 273, 235, 178, 65, 39;

Anal. Calcd for $C_{21}H_{27}N_5O_2S$: C, 60.99; H, 6.58; N, 16.94; S, 7.75. Found: C, 60.86; H, 6.47; N, 16.79; S, 7.62.

(72e) 3-amino-4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,4-diazepan-1-yl]-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide which was produced in Example 72 (72d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

Pale yellow powder

Mp 104-107°C;

IR (KBr) $\nu_{max}$ 3440, 3324, 1645, 1580, 1510, 1368, 1069, 625 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 2.07-2.13 (2H, m), 3.17-3.23 (2H, m), 3.24-3.29 (2H, m), 3.46 (2H, t, J = 5.9 Hz), 3.67 (2H, t, J = 4.9 Hz), 4.13-4.14 (2H, m), 4.18-4.20 (2H, m), 6.25-6.29 (2H, m), 6.69 (1H, d, J = 8.8 Hz), 6.98 (2H, brs), 7.08 (1H, d, J = 5.4 Hz), 7.09 (2H, brs), 8.41 (1H, d, J = 5.4 Hz);

HRMS m/z calcd for $C_{21}H_{24}O_3N_5S$ 426.1600, found 426.1619;

MS (FAB) m/z: 426 $[M+H]^+$, 409, 182, 165, 120, 63;

Anal. Calcd for $C_{21}H_{23}N_5O_3S \cdot 0.50H_2O$: C, 58.05; H, 5.57; N, 16.12. Found: C, 57.96; H, 5.85; N, 15.92.

(Example 73) 3-amino-4-{4-[4-(methylsulsulfonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-133)

3-amino-4-{4-[4-(methylthio)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (68 mg, 0.16 mmol) which was produced in Example 64 (64e) was dissolved in methanol (5 mL) and was blended with an aqueous solution (5 mL) of oxone (216 mg, 0.35 mmol) and the mixture was stirred at room temperature for 18 hours. Water (10 mL) was added to the reaction liquid and the aqueous layer was extracted with a mixed solvent (3x10 mL) of methylene chloride/2-methylene chloride propanol (4:1). After the extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/methanol =20:1) and the title compound (16 mg, yield 22%) was obtained.

White powder

Mp 89-96°C;

IR (KBr) $\nu_{max}$ 3330, 1694, 1593, 1557, 1293, 1139, 772, 537 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 2.11-2.17 (2H, m), 3.00 (3H, s), 3.47 (2H, dd, J = 5.9, 7.4 Hz), 3.55-3.61 (4H, m), 3.68 (2H, t, J = 5.9 Hz), 5.83 (1H, brs), 6.69 (2H, d, J = 9.0 Hz), 6.77 (1H, d, J = 5.5 Hz), 6.88 (1H, brs), 7.70 (2H, t, J = 9.0 Hz), 8.42 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{20}H_{24}O_3N_5S_2$ 446.1321, found 446.1307;

MS (FAB) m/z: 446 $[M+H]^+$, 415, 273, 242, 165, 65.

(Example 74) 3-amino-4-{4-[4-(dimethylamino)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-104)

(74a) tert-butyl 4-(4-dimethylaminophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in J.Org.Chem. 65,1158- (2000) and the title compound was synthesized.

Pale brown liquid

IR (film) $\nu_{max}$ 2973, 1694, 1519, 1415, 1168, 930, 810 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.38 (4.5H, s), 1.44 (4.5H, s), 1.93-1.98 (2H, m), 2.81 (6H, s), 3.20 (1H, t, J = 6.3 Hz), 3.31 (1H, t, J = 6.3 Hz), 3.45-3.57 (6H, m), 6.67 (2H, d, J = 9.0 Hz), 6.76 (2H, d, J = 9.0 Hz);

HRMS m/z calcd for $C_{18}H_{30}O_2NS$ 320.2338, found 320.2338;

MS (FAB) m/z: 320 [$M^+$], 263, 182, 165, 120, 63.

(74b) 1-(4-dimethylaminophenyl)-1,4-diazepane

tert-butyl 4-(4-dimethylaminophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 74 (74a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Pale yellow powder

Mp 214-217°C (decomposition);

IR (film) $\nu_{max}$ 2934, 1520, 1472, 1323, 1194, 945, 813 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 2.32 (2H, quint, J = 5.4 Hz), 2.84 (6H, s), 3.24 (2H, t, J = 5.9 Hz), 3.33 (2H, t, J = 4.9 Hz), 3.52 (2H, t, J = 6.8 Hz), 3.73 (2H, t, J = 4.9 Hz), 6.68 (2H, d, J = 9.3 Hz), 6.76 (2H, d, J = 9.3 Hz);

HRMS m/z calcd for $C_{13}H_{21}N_3$ 219.1737, found 219.1752;

MS (EI) m/z: 219 [$M^+$], 189, 176, 163, 148, 134, 120.

(74c) (2Z)-2-cyano-3-[4-(4-dimethylaminophenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(4-dimethylaminophenyl)-1,4-diazepane which was produced in Example 74 (74b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Pale yellow powder

Mp 161-164°C (decomposition);

IR (KBr) $\nu_{max}$ 3439, 3314, 3154, 2178, 1601, 1518, 1442, 1292, 1218, 1015, 877, 816 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.91-1.95 (2H, m), 2.26 (3H, s), 2.74 (6H, s), 3.41 (2H, t, J = 5.9 Hz), 3.51 (2H, t, J = 5.9 Hz), 3.58-3.62 (4H, m), 6.67 (2H, d, J = 9.8 Hz), 6.71 (2H, d, J = 9.8 Hz), 8.28 (1H, brs), 8.96 (1H, brs);

HRMS m/z calcd for $C_{18}H_{26}N_5S$ 344.1909, found 344.1901;

MS (EI) m/z: 343 [$M^+$], 309, 218, 182, 65;

Anal. Calcd for $C_{18}H_{25}N_5S$: C, 62.94; H, 7.34; N, 20.39; S, 9.34. Found: C, 62.66; H, 7.06; N, 20.28, S, 9.11.

(74d) 4-{4-[4-(dimethylaminophenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-[4-(4-dimethylaminophenyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 74 (74c) was used in place of (2Z)-2-cyano-3-(isobutylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 5 (5b) and the title compound was obtained.

Pale brown powder

Mp 186-188°C;

IR (KBr) $\nu_{max}$ 2948, 2204, 1625, 1517, 1243, 1142, 929, 810 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.92-1.95 (2H, m), 2.73 (6H, s), 3.42 (2H, t, J = 5.9 Hz), 3.63 (2H, t, J = 4.9 Hz), 3.71 (2H, t, J = 5.4 Hz), 3.93 (2H, t, J = 5.4 Hz), 6.42 (1H, d, J = 7.8 Hz), 6.66 (2H, d, J = 9.3 Hz), 6.69 (2H, d, J = 9.3 Hz), 7.35 (1H, d, J = 7.8 Hz), 12.52 (1H, brs);

HRMS m/z calcd for $C_{19}H_{24}N_5S$ 354.1753, found 354.1772;

MS (FAB) m/z: 353 [$M^+$], 182, 165, 65.

(74e) 3-amino-4-{4-[4-(dimethylamino)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

4-{4-[4-(dimethylaminophenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 74 (74d) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

White powder

Mp 174-176°C;

IR (KBr) $\nu_{max}$ 3438, 3324, 2944, 1644, 1579, 1517, 1368, 1230, 940, 811 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.07-2.12 (2H, m), 2.75 (6H, s), 3.20-3.25 (2H, m), 3.26-3.30 (2H, m), 3.47 (2H, t, J = 5.9 Hz), 3.67 (2H, t, J = 4.4 Hz), 6.71 (4H, s), 6.97 (2H, brs), 7.07-7.08 (3H, m), 8.40 (1H, d, J = 5.4 Hz);

HRMS m/z calcd for $C_{21}H_{27}ON_6S$ 411.1967, found 411.1945;

MS (FAB) m/z: 411 $[M+H]^+$, 394, 273, 242, 200, 189, 175, 93;

Anal. Calcd for $C_{21}H_{26}N_6OS \cdot 0.16H_2O$: C, 61.01; H, 6.42; N, 20.33; S, 7.76. Found: C, 60.75; H, 6.34; N, 20.20; S, 7.94.

(Example 75) 3-amino-6-methyl-4-(4-phenylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-76)

(75a) (1-ethoxyethylidene)malononitrile

An acetic acid (1 mL) solution of malononitrile (4.41 g, 66.8 mmol) and orthotriethyl acetate (14.7 mL, 80.2 mmol) was stirred at 80°C for one hour. The reaction liquid was cooled to room temperature and generated powder was separated by filtration and the title compound (7.14 g, yield 79%) was obtained.

White powder

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.32 (3H, t, J = 7.0 Hz), 2.45 (3H, s), 4.42 (2H, q, J = 7.0 Hz).

(75b) [1-(4-phenylpiperazin-1-yl)ethylidene]malononitrile

1-phenylpiperazine (1.68 mL, 11 mmol) was added to an ethanol (40 mL) suspension of (1-ethoxyethylidene)malononitrile (1.36 g, 10 mmol) which was produced in Example 75 (75a) and the mixture was stirred at room temperature for 15 hours. The powder which was generated was separated by filtration and the title compound (1.74 g, yield 69%) was obtained.

White powder

Mp 188-190°C;

IR (KBr) $\nu_{max}$ 2199, 1560, 1450, 1236, 998, 763 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 2.32 (3H, s), 3.32-3.34 (4H, m), 3.88 (4H, brs), 6.78 (1H, t, J = 8.6 Hz), 6.91 (2H, d, J = 8.6 Hz), 7.22 (2H, t, J = 8.6 Hz);

HRMS m/z calcd for $C_{15}H_{16}N_4$ 252.1375, found 252.1372;

MS (EI) m/z: 252 [$M^+$], 210, 160, 146, 132, 126, 119, 105, 91, 77, 65;

Anal. Calcd for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21. Found: C, 71.16; H, 6.41; N, 22.25.

(75c) [(2E)-3-(dimethylamino)-1-(4-phenylpiperazin-1-yl)but-2-enylidene]malononitrile

A xylene (10 mL) suspension of [1-(4-phenylpiperazin-1-yl)ethylidene]malononitrile which was produced in Example 75 (75b) (1.74 g, 6.9 mmol) was blended with dimethylacetamide dimethylacetal (5.0 mL, 34.5 mmol) and heated for four hours under reflux. The reaction liquid was concentrated and the obtained residue was purified by silica gel column chromatography (100% ethyl acetate) and the obtained solid was further washed with ether and the title compound (1.23 g, yield 55%) was obtained.

Yellow powder

Mp 181-184°C;

IR (KBr) $\nu_{max}$ 2193, 1557, 1511, 1440, 1375, 1258, 1023, 765, 551 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.18 (3H, s), 3.04 (6H, s), 3.24 (4H, t, J = 5.1 Hz), 3.68 (4H, t, J = 5.1 Hz), 4.53 (1H, s), 6.81 (1H, t, J = 7.8 Hz), 6.95 (2H, d, J = 7.8 Hz), 7.24 (2H, t, J = 7.8 Hz);

HRMS m/z calcd for $C_{19}H_{23}N_5$ 321.1953, found 321.1938;

MS (EI) m/z: 321 [$M^+$], 277, 256, 189, 160, 132, 72;

Anal. Calcd for $C_{19}H_{23}N_5$: C, 71.00; H, 7.21; N, 21.79. Found: C, 71.03; H, 7.21; N, 21.60.

(75d) 6-methyl-2-oxo-4-(4-phenylpiperazin-1-yl)-1,2-dihydropyridine-3-carbonitrile

[(2E)-3-(dimethylamino)-1-(4-phenylpiperazin-1-yl)but-2-enylidene]malononitrile (1.22 g, 3.8 mmol) which was produced in Example 75 (75c) was dissolved in a mixed solvent (10 mL) of acetic acid/water (4:1) and heated for one hour under reflux. The reaction liquid was cooled to room temperature and water (10 mL) was added and powder which was generated was separated by filtration and the title compound (0.87 g, yield 85%) was obtained.

Yellow powder

Mp >270°C;

IR (KBr) $\nu_{max}$ 2837, 2202, 1618, 1497, 1447, 1230, 1003, 755 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.14 (3H, s), 3.27 (4H, t, J = 5.1 Hz), 3.76 (4H, t, J = 5.1 Hz), 6.02 (1H, s), 6.81 (1H, t, J = 7.8 Hz), 6.96 (2H, d, J = 7.8 Hz), 7.24 (2H, t, J = 7.8 Hz), 11.40 (1H, brs);

HRMS m/z calcd for $C_{17}H_{18}ON_4$ 294.1481, found 294.1477;

MS (EI) m/z: 294 [$M^+$], 276, 252, 189, 162, 132, 105, 91, 77;

Anal. Calcd for $C_{17}H_{18}N_4O \cdot 0.16H_2O$: C, 68.69; H, 6.21; N, 18.85. Found: C, 69.00; H, 6.16; N, 18.49.

(75e) 2-chloro-6-methyl-4-(4-phenylpiperazin-1-yl)nicotinonitrile

N,N-dimethylaniline (75 μL, 0.53 mmol) and phosphorus oxychloride (1.6 mL, 17.4 mmol) were added to 1,4-dioxane (3 mL) solution of 6-methyl-2-oxo-4-(4-

phenylpiperazin-1-yl)-1,2-dihydropyridine-3-carbonitrile (223 mg, 0.76 mmol) which was produced in Example 75 (75d), and heated under reflux for two hours. After the reaction liquid was concentrated and a sodium hydrogen carbonate aqueous solution (10 mL) to the obtained residual substance, the aqueous layer was extracted with ethyl acetate (3x10 mL) and after the extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate =2:1) and the title compound (117 mg, yield 49%) was obtained.

Yellow powder

Mp 139-140°C;

IR (KBr) $\nu_{max}$ 2830, 2216, 1582, 1502, 1447, 1229, 989, 758, 695 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 2.49 (3H, s), 3.36 (4H, t, J = 5.1 Hz), 3.68 (4H, t, J = 5.1 Hz), 6.57 (1H, s), 6.89-6.95 (3H, m), 7.29 (2H, dd, J = 7.1, 8.6 Hz);

HRMS m/z calcd for $C_{17}H_{17}N_4Cl$ 312.1142, found 312.1147;

MS (EI) m/z: 312 [$M^+$], 294, 270, 206, 194, 179, 152, 132, 105, 91, 77;

Anal. Calcd for $C_{17}H_{17}ClN_4$: C, 65.28; H, 5.48; N, 17.91. Found: C, 65.11; H, 5.14; N, 17.69.

(75f) 3-amino-6-methyl-4-(4-phenylpiperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

2-mercaptoacetamide (about 70% purity) (48 mg, 0.52 mmol) and 8N aqueous solution of sodium hydroxide (0.1 mL) were added to N,N-dimethylformamide (0.6 mL) solution of 2-chloro-6-methyl-4-(4-phenylpiperazin-1-yl)nicotinonitrile (92 mg, 0.29 mmol) which was produced in Example 75 (75e) and the mixture was stirred at room temperature for one hour. Water was added to the reaction solution and the deposited crystal was separated by filtration and the title compound was obtained 90 mg (yield 84%).

Pale yellow crystal

Mp 247-250°C;

IR (KBr) $\nu_{max}$ 3435, 2828, 1651, 1581, 1494, 1365, 1223, 993, 762, 694 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.50 (3H, s), 2.88-3.70(8H, m), 6.80 (1H, t, J = 7.4 Hz), 6.90 (2H, brs), 6.95 (1H, s), 7.00 (2H, d, J = 7.4 Hz), 7.04 (2H, brs), 7.23 (2H, t, J = 7.4 Hz);

HRMS m/z calcd for $C_{19}H_{21}ON_5S$ 367.1467, found 367.1450;

MS (EI) m/z: 367 [$M^+$], 262, 244, 230, 218, 190, 175, 132, 120, 104, 91, 77;

Anal. Calcd for $C_{19}H_{21}N_5OS$: C, 62.10; H, 5.76; N, 19.06. Found: C, 62.38; H, 5.84; N, 18.84.

(Example 76) 3-amino-4-[4-(4-fluorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-89)

(76a) tert-butyl 4-(4-fluorophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett. 4,581-584 (2002) and the title compound was synthesized.

White powder (yield 45%)

Mp 88-89°C;

IR (KBr) $\nu_{max}$ 2968, 2921,1682, 1515, 1418, 1244, 828 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.36 (4.5H, s), 1.43 (4.5H, s), 1.90-2.01 (2H, m), 3.21 (1H, t, J = 5.9 Hz), 3.32 (1H, t, J = 5.9Hz), 3.46-3.63 (6H, m), 6.61 (2H, dd, J = 9.4, 4.3 Hz), 6.92 (2H, t, J = 8.6 Hz);

MS (EI) m/z: 294 [$M^+$], 238, 223, 193;

Anal. Calcd for $C_{16}H_{23}FN_2O_2 \cdot 0.14H_2O$: C, 64.73; H, 7.90; N, 9.44; F, 6.40. Found: C, 64.77; H, 7.92; N, 9.36; F, 6.37.

(76b) 1-(4-fluorophenyl)-1,4-diazepane

tert-butyl 4-(4-fluorophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 76 (76a) was used in place of tert-butyl 4-phenyl-1,4-

diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Pale yellow oil (yield 81%)

IR (film) $\nu_{max}$ 3322, 2935, 1611, 1513, 1228, 814 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.89 (2H, quint, J = 5.9 Hz), 2.83 (2H, t, J = 5.9 Hz), 3.02 (2H, t, J = 5.4 Hz), 3.51 (2H, t, J = 5.4 Hz), 3.54 (2H, t, J = 6.3 Hz), 6.61 (2H, dd, J = 9.3, 4.4 Hz), 6.91 (2H, t, J = 9.3 Hz);

MS (EI) m/z: 194 [$M^+$], 164, 152, 138.

(76c) (2Z)-2-cyano-3-[4-(4-fluorophenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(4-fluorophenyl)-1,4-diazepane which was produced in Example 76 (76b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Yellow ocher powder (yield 30%)

Mp 150-152°C;

IR (KBr) $\nu_{max}$ 3356, 3269, 3178, 2177, 1615, 1537, 1507 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.89-1.98 (2H, m), 2.23 (3H, s), 3.47-3.54 (4H, m), 3.57-3.63 (2H, m), 3.66-3.72 (2H, m), 6.74 (2H, dd, J = 9.0, 4.3 Hz), 6.97 (2H, t, J = 9.0 Hz), 8.31 (1H, bs), 8.96 (1H, bs);

MS (FAB) m/z: 319 $[M+H]^+$, 273, 259, 242;

Anal. Calcd for $C_{16}H_{19}FN_4S \cdot 0.4H_2O$: C, 59.02; H, 6.13; N, 17.21. Found: C, 58.73; H, 5.84; N, 17.20.

(76d) (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-fluorophenyl)-1,4-diazepan-1-yl]but-2-enethioamide

(2Z)-2-cyano-3-[4-(4-fluorophenyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 76 (76c) was used in place of (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was

performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Yellow powder (yield 73%)

Mp 127-128°C (decomposition);

IR (KBr) $\nu_{max}$ 2924, 2182, 1610, 1510, 1421, 1395, 1324, 1293 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.93-2.02 (2H, m), 2.47 (3H, s), 2.92 (3H, s), 3.14 (3H, s), 3.53 (2H, t, J = 5.9 Hz), 3.73 (2H, t, J = 5.9 Hz), 3.78 (4H, bs), 6.76 (2H, dd, J = 9.0, 4.3 Hz), 6.97 (2H, t, J = 9.0 Hz), 8.45 (2H, s);

MS (FAB) m/z: 374 $[M+H]^+$, 340, 273, 195;

Anal. Calcd for $C_{19}H_{24}FN_5S$: C, 61.10; H, 6.48; N, 18.75; F, 5.09; S, 8.59. Found: C, 61.01; H, 6.49; N, 18.50; F, 5.17; S, 8.56.

(76e) 3-amino-4-[4-(4-fluorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-fluorophenyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 76 (76d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

Pale yellow powder (yield 64%)

Mp 203-205°C;

IR (KBr) $\nu_{max}$ 3453, 3324, 3179, 2948, 2838, 1646, 1579, 1510, 1369 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.10-2.19 (2H, m), 3.16-3.24 (2H, m), 3.30 (2H, s), 3.49-3.56 (2H, m), 3.71-3.78 (2H, m), 6.76 (2H, dd, J = 9.0, 4.4 Hz), 6.96-7.05 (4H, m), 7.06-7.12 (3H, m), 8.40 (1H, d, J = 4.9 Hz);

MS (FAB) m/z: 386 $[M+H]^+$, 369, 273;

Anal. Calcd for $C_{19}H_{20}FN_5OS \cdot 1.35H_2O$: C, 57.95; H, 5.81; N, 17.78; F, 4.82; S, 8.14. Found: C, 57.58; H, 5.41; N, 17.76; F, 4.73; S, 7.99.

(Example 77) 3-amino-4-[4-(4-methylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-111)

(77a) tert-butyl 4-(4-methylphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Colourless oil (yield 36%)

IR (film) $\nu_{max}$ 2974, 2929, 1695, 1619, 1521, 1415, 1365, 1237, 1169 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.38 (4.5H, s), 1.44 (4.5H, s), 1.91-2.01 (2H, m), 2.23 (3H, s), 3.18 (1H, t, J = 5.9 Hz), 3.20 (1H, t, J = 5.9 Hz), 3.46-3.59 (6H, m), 6.60 (2H, d, J = 8.2 Hz), 7.00 (2H, d, J = 8.2 Hz);

MS (EI) m/z: 290 [$M^+$], 234, 146.

(77b) 1-(4-methylphenyl)-1,4-diazepane

tert-butyl 4-(4-methylphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 77 (77a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Pale yellow oil (yield 100%)

IR (film) $\nu_{max}$ 3318, 2923, 1618, 1520, 1394, 1363, 1189, 802 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.89 (2H, quint, J = 5.9 Hz), 2.23 (3H, s), 2.79-2.85 (2H, m), 2.99-3.05 (2H, m), 3.49-3.58 (4H, m), 6.60 (2H, d, J = 8.2 Hz), 7.00 (2H, d, J = 8.2 Hz);

MS (EI) m/z: 190 [$M^+$], 160, 148, 134.

(77c) 4-[4-(4-methylphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

1-(4-methylphenyl)-1,4-diazepane (463 mg, 2.39 mmol) which was produced in Example 77 (77b) and (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J. Org.Chem. (1962), 27,2433-2439) (386 mg, 2.27 mmol) were dissolved in N,N-dimethylformamide (4.78 mL) and the mixture was stirred at room temperature for 30 minutes. Subsequently N,N-dimethylformamide dimethylacetal (302 μL, 2.27 mmol) was added and the reaction mixture was stirred at 60°C after stirring at room temperature for 30 minutes for one hour. After cooling to room temperature, the reaction mixture was blended with ethyl acetate (10 mL) and water (50 mL) and the mixture was stirred. The deposited solid was separated by filtration and washed with ethyl acetate and water sequentially and 125 mg of the title compound was obtained. Yield 28% from 1-(4-methylphenyl)-1,4-diazepane.

Pale brown powder

Mp 220-223°C;

IR (KBr) $\nu_{max}$ 3115, 2940, 2205, 1626, 1518, 1250, 928,798, 775 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 2.11 (2H, quint, J = 5.9 Hz), 2.25 (3H, s), 3.56 (2H, t, J = 5.9 Hz), 3.71-3.76 (2H, m), 3.76-3.80 (2H, m), 4.10-4.15 (2H, m), 6.19 (1H, d, J = 7.8 Hz), 6.65 (2H, d, J = 8.2 Hz), 7.05 (2H, d, J = 8.2 Hz), 7.20 (1H, d, J = 7.8 Hz), 11.22 (1H, bs);

MS (EI) m/z: 324 [$M^+$], 160, 146;

Anal. Calcd for $C_{18}H_{20}N_4S \cdot 0.1H_2O$: C, 66.27; H, 6.24; N, 17.17; S, 9.83. Found: C, 66.07; H, 6.19; N, 17.10; S, 9.60.

(77d) 3-amino-4-[4-(4-methylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-methylphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 77 (77c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was

performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Pale brown powder (yield 28%)

Mp 175-176°C;

IR (KBr) $\nu_{max}$ 3429,3317, 3170, 3093, 2942, 2833, 1635, 1579, 1520, 1372 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.07-2.16 (2H, m), 2.18 (3H, s), 3.15-3.22 (2H, m), 3.23-3.30 (2H, m), 3.51 (2H, t, J = 6.3 Hz), 3.72 (2H, t, J = 4.7 Hz), 6.66 (2H, d, J = 8.2 Hz), 6.92-6.99 (4H, m), 7.02-7.09 (3H, m), 8.37 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 382 $[M+H]^+$, 365, 275;

Anal. Calcd for $C_{20}H_{23}N_5OS$: C, 62.97; H, 6.08; N, 18.36; S, 8.41. Found: C, 62.58; H, 6.02; N, 18.23; S, 8.29.

(Example 78) 3-amino-4-[4-(3-chlorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-93)

(78a) tert-butyl 4-(3-chlorophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

Colourless oil (yield 30%)

IR (film) $\nu_{max}$ 2975, 1694, 1594, 1493, 1416, 1365, 1237,1168 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.36 (4.5H, s), 1.44 (4.5H, s), 1.95 (2H, quint, J = 6.3 Hz), 3.21 (1H, t, J = 5.9 Hz), 3.31 (1H, t, J = 5.9 Hz), 3.46-3.60 (6H, m), 6.54 (1H, dd, J = 9.0, 2.0 Hz), 6.58-6.65 (2H, m), 7.08 (1H, t, J = 8.6 Hz);

MS (EI) m/z: 310 $[M^+]$, 253, 166.

(78b) 1-(3-chlorophenyl)-1,4-diazepane

tert-butyl 4-(3-chlorophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 78 (78c) was used in place of tert-butyl 4-phenyl-1,4-

diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Pale brown oil (yield 100%)

IR (film) $\nu_{max}$ 3323, 2933, 1593,1494, 1362, 1102, 984, 759, 683 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.89 (2H, quint, J = 5.9 Hz), 2.79-2.86 (2H, m), 2.98-3.06 (2H, m), 3.52 (2H, t, J = 5.5 Hz), 3.56 (2H, t, J = 6.3 Hz), 6.56 (1H, dd, J = 8.6, 2.7 Hz), 5.59-6.63 (1H, m), 6.67-6.64 (1H, m), 7.10 (1H, t, J = 8.6 Hz);

MS (EI) m/z: 210 [$M^+$], 168, 154.

(78c) (2Z)-3-[4-(3-chlorophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide

1-(3-chlorophenyl)-1,4-diazepane which was produced in Example 78 (78b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Slightly brown powder (yield 62%)

Mp 133-134°C;

IR (KBr) $\nu_{max}$ 3320, 3152, 2964, 2187, 1593, 1541, 1488, 1390, 1346 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.88-1.97 (2H, m), 2.24 (3H, s), 3.48-3.57 (4H, m), 3.58-3.63 (2H, m), 3.70-3.75 (2H, m), 6.60 (1H, dd, J = 8.2, 1.6 Hz), 6.70 (1H, dd, J = 8.2, 2.3 Hz), 6.75-6.78 (1H, m), 7.14 (1H, t, J = 8.2 Hz), 8.36 (1H, bs), 9.01 (1H, s);

MS (FAB) m/z: 335 $[M+H]^+$, 246, 200.

(78d) (2Z)-3-[4-(3-chlorophenyl)-1,4-diazepan-1-yl]-2-cyano-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide

(2Z)-3-[4-(3-chlorophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 78 (78c) was used in place of (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Yellow powder (yield 89%)

Mp 129-130°C (decomposition);

IR (KBr) $\nu_{max}$ 2924, 2925, 2177, 1609, 1397, 1325, 1290 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.92-2.01 (2H, m), 2.49 (3H, s), 3.15 (3H, s), 3.32 (3H, s), 3.57 (2H, t, J = 5.5 Hz), 3.72 (2H, t, J = 5.5 Hz), 3.75-3.80 (2H, m), 3.80-3.84 (2H, m), 6.61 (1H, d, J = 8.3 Hz), 6.73 (1H, dd, J = 8.3, 2.0 Hz), 6.79 (1H, s), 7.14 (1H, t, J = 8.3 Hz), 8.45 (1H, s);

MS (FAB) m/z: 390 $[M+H]^+$, 356, 211, 180;

Anal. Calcd for $C_{19}H_{24}ClN_5S$: C, 58.52; H, 6.20; N, 17.96; Cl, 9.09; S, 8.22. Found: C, 58.26; H, 6.18; N, 17.83; F, 8.95; S, 8.22.

(78e) 3-amino-4-[4-(3-chlorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-3-[4-(3-chlorophenyl)-1,4-diazepan-1-yl]-2-cyano-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide which was produced in Example 78 (78d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

Slightly brown powder (yield 61%)

Mp 213-215°C;

IR (KBr) $\nu_{max}$ 3442, 3324, 3183, 2950, 2836, 1644, 1593, 1494, 1369 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.10-2.20 (2H, m), 3.13-3.24 (2H, m), 3.25-3.31 (2H, m), 3.51-3.58 (2H, m), 3.77 (2H, t, J = 4.4 Hz), 6.62 (1H, dd, J = 8.3, 2.0 Hz), 6.73 (1H, dd, J = 8.3, 2.0 Hz), 7.01 (1H, bs), 7.06-7.12 (3H, m), 7.17 (1H, t, J = 8.3 Hz), 8.40 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 402 $[M+H]^+$, 385, 273;

Anal. Calcd for $C_{19}H_{20}N_5ClOS \cdot 0.18H_2O$: C, 56.33; H, 5.07; N, 17.29; Cl, 8.75; S, 7.91. Found: C, 56.33; H, 5.01; N, 17.38; Cl, 8.77; S, 7.68.

(Example 79) 3-amino-4-{4-[4-(benzyloxy)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-134)

(79a) tert-butyl 4-[4-(benzyloxy)phenyl]-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Colourless oil (yield 15%)

IR (film) $\nu_{max}$ 2974, 1693, 1512, 1416, 1237, 1168 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.37 (4.5H, s), 1.44 (4.5H, s), 1.90-2.00 (1H, m), 3.17-3.23 (1H, m), 3.27-3.35 (1H, m), 3.41-3.61 (6H, m), 4.97 (2H, s), 6.62 (2H, d, J = 8.8 Hz), 6.86 (2H, d, J = 8.8 Hz), 7.26-7.44 (5H, m);

MS (EI) m/z: 382 [$M^+$], 327, 291, 235.

(79b) 1-[4-(benzyloxy)phenyl]-1,4-diazepane

tert-butyl 4-[4-(benzyloxy)phenyl]-1,4-diazepane-1-carboxylate which was produced in Example 79 (79a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Pale brown oil (yield 100%)

IR (film) $\nu_{max}$ 3329, 3033, 1512, 1455, 1237, 1025, 812 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.88 (2H, quint, J = 5.9 Hz), 2.82 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.5 Hz), 3.46-3.54 (4H, m), 4.98 (2H, s), 6.62 (2H, d, J = 9.0 Hz), 6.86 (2H, d, J = 9.0 Hz), 7.25-7.43 (5H, m);

MS (EI) m/z: 282 [$M^+$], 191, 148.

(79c) 4-{4-[4-(benzyloxy)phenyl]-1,4-diazepan-1-yl}-2-thieno-1,2-dihydropyridine-3-carbonitrile

1-[4-(benzyloxy)phenyl]-1,4-diazepane which was produced in Example 79 (79b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Pale brown powder (yield 30%)

Mp 190-191°C;

IR (KBr) $\nu_{max}$ 3129, 3045, 2953, 2205, 1625, 1511, 1455, 1240 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.87-1.98 (2H, m), 3.45 (2H, t, J = 5.9 Hz), 3.62-3.75 (4H, m), 3.89-3.96 (2H, m), 4.96 (2H, s), 6.41 (1H, d, J = 7.8 Hz), 6.70 (2H, d, J - 9.0 Hz), 6.83 (2H, d, J = 9.0 Hz), 7.26-7.42 (6H, m);

MS (FAB) m/z: 417 $[M+H]^+$, 325, 200;

Anal. Calcd for $C_{24}H_{24}N_4OS \cdot 0.54H_2O$: C, 67.62; H, 5.93; N, 13.14; S, 7.52. Found: C, 67.30; H, 5.97; N, 13.50; S, 7.39.

(79d) 3-amino-4-{4-[4-(benzyloxy)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

4-{4-[4-(benzyloxy)phenyl]-1,4-diazepan-1-yl}-2-thieno-1,2-dihydropyridine-3-carbonitrile which was produced in Example 79 (79c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly brown powder (yield 89%)

Mp 211-213°C;

IR (KBr) $\nu_{max}$ 3430, 3320, 3167, 2945, 1646, 1579, 1511, 1367, 1230 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.06-2.16 (2H, m), 3.15-3.22 (2H, m), 3.24-3.30 (2H, m), 3.44-3.51 (2H, m), 3.65-3.72 (2H, m), 4.99 (2H, s), 6.69 (2H, d, J = 9.0 Hz), 6.86 (2H, d, J = 9.0 Hz), 6.98 (2H, bs), 7.05 (1H, d, J = 5.1 Hz), 7.07 (2H, bs), 7.26-7.43 (5H, m), 8.37 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 474 $[M+H]^+$, 242, 200;

Anal. Calcd for $C_{26}H_{27}N_5O_2S \cdot 0.26H_2O$: C, 65.29; H, 5.80; N, 14.64; S, 6.70. Found: C, 65.46; H, 6.02; N, 14.59; S, 6.51.

(Example 80) 3-amino-4-[4-(3-nitrophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-96)

(80a) tert-butyl 4-(3-nitrophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Orange oil (yield 25%)

IR (film) $\nu_{max}$ 2975, 1692, 1528, 1347, 1166, 735 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.33 (4.5H, s), 1.41 (4.5H, s), 1.98 (2H, quint, J = 5.9 Hz), 3.21-3.26 (1H, m), 3.31-3.37 (1H, m), 3.56-3.66 (6H, m), 6.94 (1H, dd, J = 8.2, 2.0 Hz), 7.30 (1H, t, J = 8.2 Hz), 7.44-7.50;

MS (FAB) m/z: 321 $[M^+]$, 266, 248, 222.

(80b) 1-(3-nitrophenyl)-1,4-diazepane

tert-butyl 4-(3-nitrophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 80 (80a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Reddish orange oil (yield 100%)

IR (film) $\nu_{max}$ 2935, 2855, 1618, 1525, 1347, 735 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.93 (2H, quint, J = 5.9 Hz), 2.85 (2H, t, J = 5.9 Hz), 3.06 (2H, t, J = 5.4 Hz, 3.60 (2H, t, J = 5.4 Hz), 3.64 (2H, t, J = 5.9 Hz), 6.95 (1H, dd, J = 8.3, 2.4 Hz), 7.31 (1H, t, J = 8.3 Hz), 7.44-7.51 (2H, m);

MS (EI) m/z: 221 $[M^+]$, 179, 165.

(80c) (2Z)-2-cyano-3-[4-(3-nitrophenyl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(3-nitrophenyl)-1,4-diazepane which was produced in Example 80 (80b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.
Orange powder (yield 71%)
Mp 157-158°C;
IR (KBr) $\nu_{max}$ 3443, 3353, 3277, 3176, 2926, 2182, 1617, 1525, 1346 $cm^{-1}$;
$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.92-2.01 (2H, m), 2.24 (3H, s), 3.53-3.58 (2H, m), 3.62-3.69 (4H, m), 3.81-3.88 (2H, m), 7.20-7.26 (1H, m), 7.40-7.50 (3H, m), 8.40 (1H, bs), 9.05 (1H, bs);
MS (FAB) m/z: 346 $[M+H]^+$, 246, 200.

(80d) 3-amino-4-[4-(3-nitrophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-[4-(3-nitrophenyl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 80 (80c) was used in place of (2Z)-2-cyano-3-(propylamino)but-2-enethioamide and the reaction was performed in a similar method as described in Example 4 (4b) and the title compound was obtained.
Pale yellow powder (yield 6%)
Mp 180-185°C;
IR (KBr) $\nu_{max}$ 3450, 3324, 3169, 2953, 2842, 1646, 1579, 1524,1368, 1345 $cm^{-1}$;
$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 2.16-2.24 (2H, m), 3.15-3.24 (2H, m), 3.29-3.38 (2H, m), 3.64 (2H, t, J = 5.9 Hz), 3.84-3.89 (2H, m), 7.01 (2H, bs), 7.09 (1H, d, J = 5.4 Hz), 7.10 (2H, bs), 7.21-7.26 (1H. m), 7.44 (2H, d, J = 5.4 Hz), 8.41 (1H, d, J = 5.4 Hz);
MS (FAB) m/z: 413 $[M+H]^+$, 246, 200.

(Example 81) 3-amino-4-[4-(3-chloro-4-fluorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-91)

(81a) tert-butyl 4-(3-chloro-4-fluorophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

Colourless oil (yield 36%)

IR (film) $\nu_{max}$ 2976, 1693, 1508, 1417, 1237, 1168 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.36 (4.5H, s), 1.43 (4.5H, s), 1.89-1.98 (2H, m), 3.21 (1H, t, J = 5.9 Hz), 3.32 (1H, t, J = 5.9 Hz), 3.41-3.61 (6H, m), 6.48 (1H, dt, J = 9.0, 3.3 Hz), 6.59-6.65 (1H, m), 6.96 (1H, t, J = 9.0 Hz);

MS (FAB) m/z: 328 [$M^+$], 273, 229, 189.

(81b) 1-(3-chloro-4-fluorophenyl)-1,4-diazepane

tert-butyl 4-(3-chloro-4-fluorophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 81 (81a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Slightly brown oil (yield 100%)

IR (film) $\nu_{max}$ 2934, 1611, 1508, 1240, 1047, 797 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.88 (2H, quint, J = 5.9 Hz), 2.83 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.5 Hz), 3.48 (2H, t, J = 5.5 Hz), 3.52 (2H, t, J = 5.9 Hz), 6.49 (1H, dt, J = 9.0, 3.1 Hz), 6.64 (1H, q, J = 3.1 Hz), 6.97 (1H, t, J = 9.0 Hz);

MS (EI) m/z: 228 [$M^+$], 186, 172.

(81c) (2Z)-3-[4-(3-chloro-4-fluorophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide

1-(3-chloro-4-fluorophenyl)-1,4-diazepane which was produced in Example 81 (81b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Slightly yellow powder (yield 63%)

Mp 148-150°C;

IR (KBr) $\nu_{max}$ 3358, 3265, 3170, 2177, 1615, 1526, 1505, 1408 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.89-1.96 (2H, m), 2.25 (3H, s), 3.49-3.56 (4H, m), 3.58-3.64 (2H, m), 3.68-3.75 (2H, m), 6.73 (1H, dt, J = 9.0, 3.1 Hz), 6.90 (1H, q, J = 3.1 Hz), 7.18 (1H, t, J = 9.0 Hz), 8.37 (1H, bs), 9.02 (1H, bs);

MS (FAB) m/z: 353 $[M+H]^+$, 200, 165.

(81d) (2Z)-3-[4-(3-chloro-4-fluorophenyl)-1,4-diazepan-1-yl]-2-cyano-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide

(2Z)-3-[4-(3-chloro-4-fluorophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 81 (81c) was used in place of (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Single yellow powder (yield 45%)

Mp 133-135°C (decomposition);

IR (KBr) $\nu_{max}$ 2924, 2177, 1609, 1506, 1398, 1326, 1289 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.91-2.00 (2H, m), 2.47 (3H, s), 2.91 (3H, s), 3.14 (3H, s) 3.50-3.58 (2H, m), 3.68-3.87 (6H, m), 6.73 (1H, dt, J = 9.0, 3.1 Hz), 6.90 (1H, q, J = 3.1 Hz), 7.15 (1H, t, J = 9.0 Hz), 8.43 (1H, s);

MS (FAB) m/z: 408 $[M+H]^+$, 374,273.

(81e) 3-amino-4-[4-(3-chloro-4-fluorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-3-[4-(3-chloro-4-fluorophenyl)-1,4-diazepan-1-yl]-2-cyano-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide which was produced in Example 81 (81d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was

performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

Pale brown powder (yield 54%)

Mp 181-184°C;

IR (KBr) $\nu_{max}$ 3326, 3095, 2834, 1636, 1579, 1506, 1373 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.09-2.19 (2H, d), 3.13-3.22 (2H, m), 3.24-3.32 (2H, m), 3.51 (2H, t, J = 5.9 Hz), 3.71-3.77 (2H, m), 6.71 (1H, dt, J = 9.0, 3.1 Hz), 6.85 (1H, q, J = 3.1 Hz), 6.99 (2H, bs), 7.06 (1H, d, J = 5.5 Hz), 7.09 (2H, bs), 7.18 (1H, t, J = 9.0 Hz), 8.38 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 420 $[M+H]^+$, 273, 176;

Anal. Calcd for $C_{19}H_{19}ClFN_5OS$: C, 54.35; H, 4.65; N, 16.68; Cl, 8.44; F, 4.52; S, 7.64. Found: C, 54.04; H, 4.43; N, 16.30; Cl, 8.33; F, 4.86; S, 8.03.

(Example 82) 3-amino-4-[4-(4-bromophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-95)

(82a) tert-butyl 4-(4-bromophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

Colourless oil (yield 27%)

IR (film) $\nu_{max}$ 2975, 1693, 1591, 1498, 1416, 1237, 1167 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.37 (4.5H, s), 1.43 (4.5H, s), 1.90-1.99 (2H, m), 3.20 (1H, t, J = 5.9 Hz), 3.31 (1H, t, J = 5.9 Hz), 3.48-3.58 (6H, m), 6.56 (2H, d, J = 8.8 Hz), 7.27 (2H, d, J = 8.8 Hz);

MS (FAB) m/z: 355 $[M+H]^+$, 255, 189.

(82b) 1-(4-bromophenyl)-1,4-diazepane

tert-butyl 4-(4-bromophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 82 (82a) was used in place of tert-butyl 4-phenyl-1,4-

diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Slightly brown oil (yield 90%)

IR (film) $\nu_{max}$ 2931, 1591, 1498, 1396, 1362, 1190, 806 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.88 (2H, quint, J = 5.9 Hz), 2.82 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.4 Hz), 3.51, t, J = 5.4 Hz), 3.55 (2H, t, J = 5.9 Hz), 6.56 (2H, d, J = 8.8 Hz), 7.26 82H, d, J = 8.8 Hz);

MS (EI) m/z: 254 [$M^+$], 212, 198.

(82c) (2Z)-3-[4-(4-bromophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide

1-(4-bromophenyl)-1,4-diazepane which was produced in Example 82 (82b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was synthesized.

Slightly yellow powder (yield 72%)

Mp 152-155°C;

IR (KBr) $\nu_{max}$ 3371, 3276, 3174, 2957, 2185, 1589, 1536,1496, 1408, 1357 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.87-1.97 (2H, m), 2.24 (3H, s), 3.48-3.57 (4H, m), 3.58-3.64 (2H, m), 3.70-3.77 (2H, m), 6.74 (2H, d, J = 8.8 Hz), 7.28 (2H, d, J = 8.8 Hz), 8.38 (1H, bs), 9.03 (1H, bs);

MS (FAB) m/z: 379 $[M+H]^+$, 273, 182.

(82d) (2Z)-3-[4-(4-bromophenyl)-1,4-diazepan-1-yl]-2-cyano-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide

(2Z)-3-[4-(4-bromophenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 82 (82c) was used in place of (2Z)-2-cyano-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58d) and the title compound was obtained.

Single yellow powder (yield 84%)

Mp 143-146°C (decomposition);

IR (KBr) $\nu_{max}$ 2925, 2176, 1611, 1497, 1397, 1328, 1290 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.91-2.00 (2H, m), 2.47 (3H, s), 2.92 (3H, s), 3.15 (3H, s), 3.55 (2H, t, J = 5.9 Hz), 3.69-3.85 (6H, m), 6.74 (2H, d, J = 8.8 Hz), 7.26 (2H, d, J = 8.8 Hz), 8.46 (1H, s);

MS (FAB) m/z: 434 $[M+H]^+$, 400, 273.

(82e) 3-amino-4-[4-(4-bromophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-3-[4-(4-bromophenyl)-1,4-diazepan-1-yl]-2-cyano-N-[(1E)-(dimethylamino)methylene]but-2-enethioamide which was produced in Example 82 (82d) was used in place of (2Z)-2-cyano-N-[(1E)-(dimethylamino)methylene]-3-[4-(4-methoxyphenyl)-1,4-diazepan-1-yl]but-2-enethioamide and the reaction was performed in a similar method as described in Example 58 (58e) and the title compound was obtained.

Slightly brown powder (yield 59%)

Mp 170-173°C;

IR (KBr) $\nu_{max}$ 3442, 3322, 3180, 2948, 2838, 1645, 1588, 1498, 1367 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.13 (2H, quint, J = 5.5 Hz), 3.13-3.21 (2H, m), 3.23-3.30 (2H, m), 3.52 (2H, t, J = 6.3 H), 3.71-3.77 (2H, m), 6.72 (2H, d, J = 9.0 Hz), 6.98 (2H, bs), 7.05 81H, d, J = 5.5 Hz), 7.08 (2H, bs), 7.27 (2H, d, J = 9.0 Hz), 8.38 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 446 $[M+H]^+$, 429, 273.

(Example 83) 3-amino-4-[4-(4-ethoxyphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-127)

(83a) tert-butyl 4-(4-ethoxyphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

Colourless oil (yield 27%)

IR (film) $\nu_{max}$ 2976, 1694, 1513, 1416, 1240,1169 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.37 (3H, t, J = 6.8 Hz), 1.38(4.5H, s), 1.44 (4.5H, s), 1.91-2.00 (2H, m), 3.21 (1H, t, J = 5.9 Hz), 3.32 (1H, t, J = 5.9 Hz), 3.45-3.60 (6H, m), 3.96 (2H, q, J = 6.8 Hz), 6.64 (2H, d, J = 9.3 Hz), 6.81 (2H, d, J = 9.3 Hz);

MS (FAB) m/z: 320 [$M^+$], 264, 219.

(83b) 1-(4-ethoxyphenyl)-1,4-diazepane

tert-butyl 4-(4-ethoxyphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 83 (83a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Brown oil (yield 98%)

IR (film) $\nu_{max}$ 2931, 1513, 1239, 1050, 812 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.37 (3H, t, J = 7.0 Hz), 1.88 (2H, quint, J = 5.9 Hz), 2.82 (2H, t, J = 5.5H), 3.01 (2H, t, J = 5.5 Hz), 3.46-3.55 (4H, m), 3.95 (2H, q, J = 7.0 Hz), 6.62 (2H, d, J = 9.4 Hz), 6.79 (2H, d, J = 9.4 Hz);

MS (EI) m/z: 220 [$M^+$], 178, 164.

(83c) 4-[4-(4-ethoxyphenyl)-1,4-diazepan-1-yl]-2-thioxa-1,2-dihydropyridine-3-carbonitrile

1-(4-ethoxyphenyl)-1,4-diazepane which was produced in Example 83 (83b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Slightly brown powder (yield 25%)

Mp 204-208°C;

IR (KBr) $\nu_{max}$ 3118, 2970, 2207, 1625, 1511, 1244 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.38 (3H, t, J = 7.0 Hz), 2.11 (2H, quint, J = 5.9 Hz), 3.50 (2H, t, J = 5.9 Hz), 3.69-3.78 (4H, m), 3.96 (2H, q, J = 7.0 Hz), 4.07-4.13 (2H, m), 6.20 (1H, d, J = 7.6 Hz), 6.66 (2H, d, J = 9.2 Hz), 6.81 (2H, d, J = 9.2 Hz), 7.22 (1H, d, J = 7.6 Hz),11.97 (1H, bs);

MS (FAB) m/z: 355 $[M+H]^+$, 273;

Anal. Calcd for $C_{19}H_{22}N_4OS \cdot 0.16H_2O$: C, 63.86; H, 6.38; N, 15.68; S, 8.97. Found: C, 63.86; H, 6.26; N, 15.66; S, 8.85.

(83d) 3-amino-4-[4-(4-ethoxyphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-ethoxyphenyl)-1,4-diazepan-1-yl]-2-thioxa-1,2-dihydropyridine-3-carbonitrile which was produced in Example 83 (83c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly brown powder (yield 84%)

Mp 181-183°C;

IR (KBr) $\nu_{max}$ 3423, 3330, 3116, 2973, 1586, 1512, 1369, 1234 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.28 (3H, t, J = 7.0 Hz), 2.08-2.16 (2H, m), 3.18-3.24 (2H, m), 3.26-3.31 (2H, m), 3.40 82H, t, J = 5.9 Hz), 3.70 82H, t, J = 4.7 hz), 3.92 (2H, q, J = 7.0 Hz), 6.71 (2H, d, J = 8.8 Hz), 6.80 (2H, d, J = 8.8 Hz), 6.99 (2H, bs), 7.05-7.12 (3H, m), 8.40 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 412 $[M+H]^+$, 75;

Anal. Calcd for $C_{21}H_{25}N_5O_2S \cdot 0.42H_2O$: C, 60.19; H, 6.21; N, 16.71; S, 7.65. Found: C, 60.49; H, 6.32; N, 16.93; S, 7.35.

(Example 84) 3-amino-4-[4-(3,4-dimethylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-116)

(84a) tert-butyl 4-(3,4-dimethylphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Colourless oil (yield 17%)

IR (film) $\nu_{max}$ 3366, 2972, 2931, 1695, 1616, 1511,1415,1242, 1169 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.36 (4.5H, s), 1.45 (4.5H, s), 1.93-2.02 (2H, m), 2.15 (3H, s), 2.22 (3H, s), 3.20 (1H, t, J = 5.9 Hz), 3.30 (1H, d, J = 5.9 Hz), 3.47-3.59 (6H, m), 6.46 (1H, d, J = 8.3 Hz), 6.51 (1H, s), 6.96 (1H, d);

MS (FAB) m/z: 304 [$M^+$], 249, 203.

(84b) 1-(3,4-dimethylphenyl)-1,4-diazepane

tert-butyl 4-(3,4-dimethylphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 84 (84a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Pale brown prism crystal (yield 100%)

IR (KBr) $\nu_{max}$ 2939, 2860, 2384, 1615, 1512, 1459, 1411, 1280 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.88 (2H, quint, J = 5.9 Hz), 2.15 (3H, s), 2.21 (3H, s), 2.82 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.5 Hz), 3.49-3.56 (4H, m), 6.45 (1H, dd, J = 8.2, 2.7 Hz), 6.50 (1H, d, J = 2.7 Hz), 6.94 (1H, d, J - 8.2 Hz);

MS (EI) m/z: 204 [$M^+$], 174, 162, 148.

(84c) 4-[4-(3,4-dimethylphenyl)-1,4-diazepan-1-yl]-2-thioxa-1,2-dihydropyridine-3-carbonitrile

1-(3,4-dimethylphenyl)-1,4-diazepane which was produced in Example 84 (84b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was

performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Pale brown powder (yield 31%)

Mp 251-253°C;

IR (KBr) $\nu_{max}$ 3121, 2937, 2205, 1625, 1511, 1459, 1254 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.93 (2H, quint, J = 5.5 Hz), 2.07 (3H, s), 2.14 (3H, s), 3.48 (2H, t, J = 5.9 Hz), 3.65-3.74 (4H, m), 3.91-3.98 (2H, m), 6.43 (1H, d, J = 7.6 Hz), 6.50 (1H, dd, J = 8.4, 2.7 Hz), 6.60 (1H, d, J = 2.7 Hz), 6.90 (1H, d, J = 8.4 Hz), 7.37 (1H, d, J = 7.6 Hz), 12.44 (1H, bs);

MS (FAB) m/z: 339 $[M+H]^+$, 273, 174;

Anal. Calcd for $C_{19}H_{22}N_4S \cdot 0.24H_2O$: C, 66.57; H, 6.61; N, 16.34; S, 9.35. Found: C, 66.47; H, 6.44; N, 16.34; S, 9.15.

(84d) 3-amino-4-[4-(3,4-dimethylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(3,4-dimethylphenyl)-1,4-diazepan-1-yl]-2-thioxa-1,2-dihydropyridine-3-carbonitrile which was produced in Example 84 (84c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly brown powder (yield 82%)

Mp 195-197°C;

IR (KBr) $\nu_{max}$ 3432, 3324, 3174, 2934, 2829, 1642, 1579, 1507, 1369 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.08-2.15 (2H, m), 2.10 (3H,s), 2.16 (3H, s), 3.15-3.22 (2H, m), 3.25-3.31 (2H, m), 3.52 (2H, t, J = 5.9 Hz), 3.69-3.76 (2H, m), 6.50 (1H, dd, J = 8.3, 2.4 Hz), 6.60 (1H, d, J = 2.4 Hz), 6.92 (1H, d, J = 8.3 Hz), 6.99 (2H, bs), 7.04-7.13 (3H, m), 8.40 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 396 $[M+H]^+$, 246, 185;

Anal. Calcd for $C_{21}H_{25}N_5OS$: C, 63.77; H, 6.37; N, 17.71; S, 8.11. Found: C, 63.45; H, 6.33; N, 17.54; S, 8.11.

(Example 85) 3-amino-4-[4-(3,4-difluorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-90)

(85a) tert-butyl 4-(3,4-difluorophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Colourless oil (yield 29%)

IR (film) $\nu_{max}$ 2976, 1691, 1521, 1417, 1234, 1168, 777 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.36 (4.5H, s), 1.43 (4.5H, s), 1.89-1.98 (2H, m), 3.21 (1H, t, J = 5.9 Hz), 3.31 (1H, t, J = 5.9 Hz), 3.41-3.58 (6H, m), 6.27-6.33 (1H, m), 6.38-6.47 (1H, m), 6.96 (1H, q, J = 9.0 Hz);

MS (FAB) m/z: 312 [$M^+$], 257, 211.

(85b) 1-(3,4-difluorophenyl)-1,4-diazepane

tert-butyl 4-(3,4-difluorophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 85 (85a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Brown oil (yield 98%)

IR (film) $\nu_{max}$ 2935, 2838, 1631, 1597, 1520, 1275, 777 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.88 (2H, m, J = 5.9 Hz), 2.83 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.4 Hz), 3.48 (2H, t, J = 5.4 Hz), 3.52 (2H, t, J = 5.9 Hz), 6.28-6.34 (1H, m), 6.44 (1H, ddd, J = 14.2, 6.8, 2.9 Hz), 6.98 (1H, q, J = 9.3 Hz);

MS (EI) m/z: 212 [$M^+$], 170, 156.

(85c) 4-[4-(3,4-difluorophenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

1-(3,4-difluorophenyl)-1,4-diazepane which was produced in Example 85 (85b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Slightly brown powder (yield 27%)

Mp 250-251°C;

IR (KBr) $\nu_{max}$ 3122, 2959, 2206, 1626, 1520, 1247, 777 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.93 (2H, quint, J = 5.9 Hz), 3.51 (2H, m), 3.68-3.76 (4H, m), 3.92-3.98 (2H, m), 6.43 (1H, d, J = 7.8 Hz), 6.52-6.57 (1H, m), 6.83 (1H, ddd, J = 14.7, 6.8, 2.9 Hz), 7.17 (1H, q, J = 9.8 Hz), 7.37 (1H, d, J = 7.8 Hz), 12.15 (1H, bs);

MS (FAB) m/z: 347 $[M+H]^+$, 273, 242;

Anal. Calcd for $C_{17}H_{16}F_2N_4S \cdot 0.2H_2O$: C, 58.34; H, 4.72; F, 10.86; N, 16.01; S, 9.16. Found: C, 58.48; H, 4.73; F, 10.59; N, 16.13; S, 9.04.

(85d) 3-amino-4-[4-(3,4-difluorophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(3,4-difluorophenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 85 (85c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly brown powder (yield 83%)

Mp 199-201°C;

IR (KBr) $\nu_{max}$ 3454, 3324, 3171, 2953, 2839, 1650, 1582, 1519, 1369 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.10-2.18 (2H, m), 3.14-3.23 (2H, m), 3.24-3.32 (2H, m), 3.52 (2H, t, J = 6.4 Hz), 3.75 (2H, t, J = 5.0 Hz), 6.49-6.56 (1H, m), 6.78

(1H, ddd, J = 14.7, 6.8, 2.9 Hz), 7.00 (2H, bs), 7.08 (1H, d, J = 5.2 Hz), 7.10 (2H, bs), 7.20 (1H, q, J = 9.8 Hz), 8.41 (1H, d, J = 5.2 Hz);

MS (FAB) m/z: 404 $[M+H]^+$, 387, 246, 200;

Anal. Calcd for $C_{19}H_{19}F_2N_5O_2S \cdot 0.24H_2O$: C, 55.96; H, 4.82; F, 9.32; N, 17.17; S, 7.86. Found: C, 55.97; H, 4.76; F, 9.25; N, 17.24; S, 7.76.

(Example 86) 3-amino-4-{4-[3-(trifluoromethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-120)

(86a) tert-butyl 4-[3-(trifluoromethyl)phenyl]-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

Colourless oil (yield 13%)

IR (film) $\nu_{max}$ 2976, 1695, 1612, 1463, 1417, 1321, 1164, 1124 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.33 (4.5H, s), 1.43 (4.5H, s), 1.93-2.01 (2H, m), 3.23 81H, t, J = 5.9 Hz), 3.34 (1H, t, J = 5.9 Hz), 3.54-3.64 (6H, m), 6.80-6.94 (3H, m), 7.23-7.32 (1H, m);

MS (FAB) m/z: 344 $[M^+]$, 289, 243.

(86b) 1-[3-(trifluoromethyl)phenyl]-1,4-diazepane

tert-butyl 4-[3-(trifluoromethyl)phenyl]-1,4-diazepane-1-carboxylate which was produced in Example 86 (86a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Brown oil (yield 89%)

IR (film) $\nu_{max}$ 2938, 1691, 1611, 1506, 1457, 1321, 1162, 1121 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.91 (2H, t, J = 5.9 Hz), 2.84 (2H, t, J = 5.9 Hz), 3.04 (2H, t, J = 5.4 Hz), 3.57 (2H, t, J = 5.4 Hz), 3.60 (2H, t, J = 6.4 Hz), 6.80-6.91 (3H, m), 7.25-7.31 (1H, m);

MS (EI) m/z: 244 [$M^+$], 202, 188.

(86c) 2-thioxo-4-{4-[3-(trifluoromethyl)phenyl]-1,4-diazepan-1-yl}-1,2-dihydropyridine-3-carbonitrile

1-[3-(trifluoromethyl)phenyl]-1,4-diazepane which was produced in Example 86 (86b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Slightly brown powder (yield 27%)

Mp 247-248°C;

IR (KBr) $\nu_{max}$ 2414, 3129, 2964, 2207, 1625, 1523, 1320, 1120 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.92-2.00 (2H, m), 3.60 (2H, t, J = 5.9 Hz), 3.75 (2H, t, J = 5.9 hz), 3.80 (2H, t, J = 5.4 Hz), 3.08 (2H, t, J = 5.4 Hz), 6.45 (1H, d, J = 7.8 Hz), 6.90 (1H, d, J = 7.3 Hz), 6.99 (1H, s), 7.07 (1H, dd, J = 8.3, 2.0 Hz), 7.33-7.40 (2H, m), 11.53 (1H, bs);

MS (FAB) m/z: 379 $[M+H]^+$, 273, 226;

Anal. Calcd for $C_{18}H_{17}F_3N_4S \cdot 0.2H_2O$: C, 56.69; H, 4.59; N, 14.67; S, 8.39. Found: C, 56.60; H, 4.58; N, 14.67; S, 8.39.

(86d) 3-amino-4-{4-[3-(trifluoromethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

2-thioxo-4-{4-[3-(trifluoromethyl)phenyl]-1,4-diazepan-1-yl}-1,2-dihydropyridine-3-carbonitrile which was produced in Example 86 (86c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly brown powder (yield 84%)

Mp 195-197°C;

IR (KBr) $\nu_{max}$ 3427, 3326, 3167, 1639, 1580, 1504, 1371, 1121 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 2.14-2.23 (2H, m), 3.15-3.25 (2H, m), 3.26-3.36 (2H, m), 3.60 (2H, t, J = 5.9 Hz), 3.84 (2H, t, J = 4.6 Hz), 6.91 (1H, d, J = 7.3 Hz), 6.95-6.99 (1H, m), 7.01 (1H, bs), 7.06 (1H, dd, J = 8.3, 2.0 Hz), 7.09 (1H, d, J = 5.2 Hz), 7.10 (1H, bs), 7.38 81H, t, J = 8.3 Hz), 8.41 (1H, d, J = 5.2 Hz);
MS (FAB) m/z: 436 $[M+H]^+$, 419, 240.

(Example 87) 3-amino-4-{4-[4-(trifluoromethoxy)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-130)

(87a) tert-butyl 4-[4-(trifluoromethoxy)phenyl]-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.
Slightly brown oil (yield 41%)
IR (film) $\nu_{max}$ 2976, 1692, 1516, 1417, 1268, 1163 $cm^{-1}$;
$^1$H NMR($CDCl_3$, 400 MHz) δ 1.33 (4.5H, s), 1.42 (4.5H, s), 1.90-1.98 (2H, m), 3.22 (1H, t, J = 5.9 Hz), 3.32 (1H, t, J = 5.5 Hz), 3.48-3.60 (6H, m), 6.61 (2H, d, J = 9.2 Hz), 7.04 (2H, d, J - 9.2 Hz);
MS (FAB) m/z: 360 $[M^+]$, 305, 259.

(87b) 1-[4-(trifluoromethoxy)phenyl]-1,4-diazepane

tert-butyl 4-[4-(trifluoromethoxy)phenyl]-1,4-diazepane-1-carboxylate which was produced in Example 87 (87a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.
Green oil (yield 57%)
IR (film) $\nu_{max}$ 2936, 1610, 1516, 1265, 1231, 1205, 1156, 805 $cm^{-1}$;
$^1$H NMR($CDCl_3$, 500 MHz) δ 1.89 (2H, quint, J = 5.9 Hz), 2.83 (2H, t, J = 5.9 Hz), 3.03 (2H, t, J = 5.4 Hz), 3.53 (2H, t, J = 5.4 Hz), 3.56 (2H, t, J = 5.9 Hz), 6.63 (2H, d, J = 9.3 Hz), 7.05 (2H, d, J = 9.3 Hz);

MS (EI) m/z: 260 [$M^+$], 218, 204.

(87c) 2-thioxa-4-{4-[4-(trifluoromethoxy)phenyl]-1,4-diazepan-1-yl}-1,2-dihydropyridine-3-carbonitrile

1-[4-(trifluoromethoxy)phenyl]-1,4-diazepane was used in place of 1-(4-methylphenyl)-1,4-diazepane which was produced in Example 87 (87b) and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Slightly brown powder (yield 19%)

Mp 240-242°C;

IR (KBr) $\nu_{max}$ 3122, 2957, 2210, 1627, 1514, 1245, 1150 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.91-1.98 (2H, m), 3.55 (2H, t, J = 5.9 Hz), 3.70-3.78 (4H, m), 3.97 (2H, t, J = 5.4 Hz), 6.44 (1H, d, J = 7.8 Hz), 6.83 (2H, d, J = 9.3 Hz), 7.13 (2H, d, J = 9.3 Hz), 7.37 (1H, d, J = 7.8 Hz), 12.53 (1H, bs);

MS (FAB) m/z: 395 $[M+H]^+$, 175;

Anal. Calcd for $C_{18}H_{17}F_3N_4OS$: C, 54.81; H, 4.34; N, 14.21; S, 8.13. Found: C, 54.74; H, 4.06; N, 14.12; S, 8.08.

(87d) 3-amino-4-{4-[4-(trifluoromethoxy)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

2-thioxa-4-{4-[4-(trifluoromethoxy)phenyl]-1,4-diazepan-1-yl}-1,2-dihydropyridine-3-carbonitrile which was produced in Example 87 (87c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly brown powder (yield 79%)

Mp 163-165°C;

IR (KBr) $\nu_{max}$ 3413, 3325, 3176, 2947, 2836, 1637, 1579, 1515, 1372 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 2.11-2.19 (2H, m), 3.16-3.24 (2H, m), 3.26-3.33 (2H, m), 3.55 (2H, t, J = 5.9 Hz), 3.79 (2H, t, J = 4.6 Hz), 6.82 (2H, d, J = 9.3 Hz), 7.00 (2H, bs), 7.08 (1H, d, J = 5.4 Hz), 7.10 (2H, bs), 7.15 (2H, d, J = 9.3 Hz), 8.40 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 452 $[M+H]^+$, 435, 216;

Anal. Calcd for $C_{20}H_{20}F_3N_5O_2S$: C, 53.21; H, 4.47; F, 12.62; N, 15.51; S, 7.10.

Found: C, 53.06; H, 4.13; F, 12.53; N, 15.44; S, 6.93.

(Example 88) 3-amino-4-[4-(2,3,5,6-tetrafluoropyridin-4-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-145)

(88a) tert-butyl 4-(2,3,5,6-tetrafluoropyridin-4-yl)-1,4-diazepane-1-carboxylate

Pentafluoropyridine (878 μL, 8 mmol), 1,4-tert-butyl diazepane-1-carboxylate (1,577 μL, 8 mmol) and triethylamine (1,227 μL, 8.8 mmol) were dissolved in methylene chloride (40 mL) and the mixture was stirred at room temperature for one hour. The reaction liquid was blended with a saturated sodium hydrogen carbonate aqueous solution (50 mL) and partitioned and the aqueous layer was extracted with methylene chloride (2x25 mL) and then the organic layer was combined and the solvent was evaporated under reduced pressure after drying over anhydrous sodium sulfate. Residual substance was purified by silica gel column chromatography (eluent: hexane/ethyl acetate =5/1) and 2.54 g (91%) of the title compound was obtained.

White powder

Mp 55-59°C;

IR (KBr) $\nu_{max}$ 2985, 1690, 1636, 1523, 1476, 1170, 1143 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.44 (4.5H, s), 1.46 (4.5H, s), 1.90-2.03 (1H, m), 3.47 (1H, m, J = 5.9 Hz, 3.53)1H, t, J = 5.9 Hz), 3.71-3.56 (6H, m);

MS (FAB) m/z: 350 $[M+H]^+$, 294, 250.

(88b) 1-(2,3,5,6-tetrafluoropyridin-4-yl)-1,4-diazepane

tert-butyl 4-(2,3,5,6-tetrafluoropyridin-4-yl)-1,4-diazepane-1-carboxylate which was produced in Example 88 (88a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

White powder (yield 97%)

Mp 58-61°C;

IR (KBr) $\nu_{max}$ 3356, 2932, 2852, 1638, 1534, 1473, 1126, 1068, 932 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.92 (2H, quint, J = 5.9 Hz), 2.96 (2H, t, J = 5.9 Hz), 3.05 (2H, t, J = 5.5 Hz), 3.62-3.71 (6H, m);

MS (EI) m/z: 249 [$M^+$], 207, 193.

(88c) 4-[4-(2,3,5,6-tetrafluoropyridin-4-yl)-1,4-diazepan-1-yl]-2-thioxa-1,2-dihydropyridine-3-carbonitrile

1-(2,3,5,6-tetrafluoropyridin-4-yl)-1,4-diazepane which was produced in Example 88 (88b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Pale brown powder (yield 22%)

Mp 267-269°C;

IR (KBr) $\nu_{max}$ 3121, 2961, 2210, 1628, 1522, 1471, 1250, 1135, 962 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.97-2.08 (2H, m), 3.58-3.66 (2H, m), 3.76-3.85 (2H, m), 3.89-3.96 (2H, m), 3.97-4.05 (2H, m), 6.50 (1H, d, J = 7.6 Hz), 7.42 (1H, d, J = 7.6 Hz), 12.51 (1H, bs);

MS (FAB) m/z: 384 $[M+H]^+$, 200;

Anal. Calcd for $C_{16}H_{13}F_4N_5S$: C, 50.13; H, 3.42; N, 18.27; S, 8.36. Found: C, 50.08; H, 3.66; N, 18.35; S, 8.37.

(88d) 3-amino-4-[4-(2,3,5,6-tetrafluoropyridin-4-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(2,3,5,6-tetrafluoropyridin-4-yl)-1,4-diazepan-1-yl]-2-thioxa-1,2-dihydropyridine-3-carbonitrile which was produced in Example 88 (88c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly yellow powder (yield 85%)

Mp 228-231°C;

IR (KBr) $\nu_{max}$ 3441, 3325, 3175, 2924, 1641, 1583, 1469, 1371, 1121, 962 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 2.14-2.23 (2H, m), 3.26-3.35 (2H, m), 3.39-3.48 (2H, m), 3.75-3.82 (2H, m), 3.87-3.94 (2H, m), 7.04 (2H, bs), 7.10 (1H, d, J = 5.4 Hz), 7.11 (2H, bs), 8.44 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 441 $[M+H]^+$, 329, 273;

Anal. Calcd for $C_{18}H_{16}F_4N_6OS$: C, 49.09; H, 3.66; F, 17.25; N, 19.08; S, 7.28.

Found: C, 49.02; H, 3.72; F, 16.85; N, 19.13; S, 7.21.

(Example 89) 3-amino-4-(4-quinazolin-4-yl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-147)

(89a) tert-butyl 4-quinazolin-4-yl-1,4-diazepane-1-carboxylate

4-chloroquinazoline (Helv. Chim. Acta, (2001), 84,1112-1118) was used in place of pentafluoropyridine and the reaction was performed in a similar method as described in Example 88 (88a) and the title compound was obtained.

Colourless oil (yield 91%)

Mp 55-59°C;

IR (film) $\nu_{max}$ 2975, 2929, 2869, 1693, 1566, 1506, 1346, 1167 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.34 (4.5H, s), 1.42 (4.5H, s), 2.03-2.21 (2H, m), 3.47 (1H, t, J = 5.9 Hz), 3.56 (1H, t, J = 5.5 Hz), 3.65-3.77 (2H, m), 3.90-4.10 (4H, m), 7.41 (1H, t, J = 8.2 Hz), 7.71 (1H, t, J = 8.2 Hz), 7.86 (1H, d, J = 8.2 Hz), 7.95 (1H, d, J = 8.2 Hz), 8.64 (1H,s);

MS (FAB) m/z: 329 $[M+H]^+$, 273.

(89b) 4-(1,4-diazepan-1-yl) quinazoline

tert-butyl 4-quinazolin-4-yl-1,4-diazepane-1-carboxylate which was produced in Example 89 (89a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Slightly brown oil (yield 76%)

IR (film) $\nu_{max}$ 3296, 2937, 1684, 1613, 1567, 1505, 1346 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400 MHz) δ 2.03 (2H, m), 2.96-3.02 (2H, m), 3.17-3.22 (2H, m), 3.98-4.04 (4H, m), 7.33-7.39 (1H, m), 7.64-7.70 (1H, m), 7.80-7.84 (1H, m), 7.92-7.97 (1H, m), 8.60 (1H,s);

MS (EI) m/z: 228 $[M^+]$, 185, 172, 159.

(89c) 4-(4-quinazolin-4-yl-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

4-(1,4-diazepan-1-yl)quinazoline produced in Example 89 (89b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Brown powder (yield 19%)

Mp 221-223°C;

IR (KBr) $\nu_{max}$ 3431, 3111, 2926, 2204, 1623, 1566, 1504, 1344, 1242 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.14-2.22 (2H, m), 3.93 (2H, t, J = 5.9 Hz), 3.98 (2H, t, J = 5.5 Hz), 4.13 (4H, bs), 6.47 (1H, d, J = 7.4 Hz), 7.35 (1H, d, J = 8.2 Hz),

7.45-7.52 (1H, m), 7.70-7.79 (2H, m), 8.02 (1H, d, J = 8.2 Hz), 8.50 (1H, s),12.49 (1H, bs);

MS (FAB) m/z: 363 $[M+H]^+$, 257, 229;

Anal. Calcd for $C_{19}H_{18}N_6S$: C, 60.09; H, 5.29; N, 22.13. Found: C, 60.18; H, 5.38; N, 22.09.

(89d) 3-amino-4-(4-quinazolin-4-yl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

4-(4-quinazolin-4-yl-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 89 (89c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly yellow powder (yield 85%)

Mp 228-231°C;

IR (KBr) $\nu_{max}$ 3439, 3321, 3181, 2957, 1648, 1567, 1501, 1344 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.24-2.36 (2H, m), 3.17-3.30 (2H, m), 3.50-3.59 (2H, m), 4.03-4.13 (2H, m), 4.18-4.29 (2H, m), 7.00 (2H, bs), 7.06 (1H, d, J = 5.1 Hz), 7.10 (2H, bs), 7.46 (1H, ddd, J = 8.6, 6.0, 2,3 Hz), 7.70-7.78 (2H, m), 8.10 (1H, d, J = 8.2 Hz), 8.39 (1H, d, J = 5.1 Hz), 8.50 (1H, s);

MS (FAB) m/z: 420 $[M+H]^+$, 273, 246, 200.

(Example 90) 3-amino-4-[4-(4-methyl-3-nitrophenyl)-1,4-diazepan-1-yl]thieno[2,3-2b]pyridine-2-carboxamide (Exemplified Compound No. 3-119)

(90a) tert-butyl 4-(4-methyl-3-nitrophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Orange powder (yield 41%)

Mp 103-106°C;

IR (KBr) $\nu_{max}$ 2978, 1685, 1528, 1415, 1334 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.35 (4.5H, s), 1.42 (4.5H, s), 1.93-2.00 (2H, m), 2.45 (3H, s), 3.23 (1H, t, J = 5.9 Hz), 3.33 (1H, t, J = 5.9 Hz), 3.53-3.62 (6H, m), 6.82 (1H, dd, J = 8.8, 2.9 Hz, 7.13 (1H, d, J = 8.8 Hz, 7.26 (1H, d, J = 2.9 Hz);

MS (FAB) m/z: 336 $[M+H]^+$, 280, 234, 189;

Anal. Calcd for $C_{17}H_{25}N_3O_4 \cdot 0.3H_2O$: C, 59.91; H, 7.57; N, 12.33. Found: C, 59.94; H, 7.29; N, 12.01.

(90b) 1-(4-methyl-3-nitrophenyl)-1,4-diazepane

tert-butyl 4-(4-methyl-3-nitrophenyl)-1,4-diazepane-1-carboxylate which was produced in Example 90 (90a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Red oil (yield 100%)

IR (liquid) $\nu_{max}$ 2930, 1628, 1527, 1346 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.91 (2H, t, J = 5.9 Hz), 2.45 (3H, s), 2.83 (2H, t, J = 5.9 Hz), 3.04 (2H, t, J = 5.5 Hz), 3.55 (2H, t, J = 5.5 Hz), 3.59 (2H, t, J = 5.9 Hz), 6.81 (1H, dd, J = 8.3, 2.9 Hz), 7.12 (1H, d, J = 8.3 Hz), 7.26 (1H, d, J = 2.9 Hz);

MS (EI) m/z: 235 $[M^+]$, 193, 179.

(90c) 4-[4-(4-methyl-3-nitrophenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

1-(4-methyl-3-nitrophenyl)-1,4-diazepane which was produced in Example 90 (90b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Brown powder (yield 31%)

Mp 277-278°C;

IR (KBr) $\nu_{max}$ 3437, 3124, 2961, 2206, 1625, 1525, 1341, 1252 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.94 (2H, m), 2.32 (3H, s), 3.57 (2H, t, J = 5.9 Hz), 3.70-3.81 (4H, m), 3.92-3.99 (2H, m), 6.42 (1H, d, J = 7.8 Hz), 7.05 (1H, dd, J = 8.6, 2.7 Hz), 7.22 (1H, d, J = 8.6 Hz), 7.24 (1H, d, J = 2.7 Hz), 7.35 (1H, d, J = 7.8 Hz), 12.47 (1H, bs);

MS (FAB) m/z: 370 $[M+H]^+$, 259, 242;

Anal. Calcd for $C_{18}H_{19}N_5O_2S \cdot 0.26H_2O$: C, 57.79; H, 5.26; N, 18.72; S, 8.57. Found: C, 57.78; H, 5.16; N, 18.73; S, 8.51.

(90d) 3-amino-4-[4-(4-methyl-3-nitrophenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-methyl-3-nitrophenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 90 (90c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Orange powder (yield 91%)

Mp 114-117°C;

IR (KBr) $\nu_{max}$ 3439, 3323, 3181, 2927, 2846, 1650, 1579, 1525, 1366 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.13-2.21 (2H, m), 2.36 (3H,s), 3.14-3.23 (2H, m), 3.27-3.34 (2H, m), 3.59 (2H, t, J = 5.9 Hz), 3.81 (2H, t, J = 4.8 Hz), 7.01 (2H, bs), 7.0-7.15 84H, m), 7.24-7.29 (2H, m), 8.41 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 427 $[M+H]^+$, 410, 273, 246;

Anal. Calcd for $C_{20}H_{22}N_6O_3S \cdot 0.5H_2O$: C, 55.16; H, 5.32; N, 19.30. Found: C, 54.87; H, 5.49; N, 19.58.

(Example 91) 3-amino-4-[4-(4-isopropoxyphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-129)

(91a) tert-butyl 4-(4-isopropoxyphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org. Lett., 4, 581-584 (2002) and the title compound was synthesized.

Colourless oil (yield 14%)

IR (film) $\nu_{max}$ 2974, 1694, 1511, 1415, 1366, 1237, 1168, 1122 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.28 (6H, d, J = 5.9 Hz), 1.37 (4.5H, s), 1.43 (4.5H, s), 1.90-2.00 (2H, m), 3.20 (2H, t, J = 5.9 Hz), 3.31 (2H, t, J = 5.5 Hz), 3.40-3.61 (6H, m), 4.35 (1H, sept, J = 5.9 Hz), 6.61 (2H, d, J = 9.0 Hz), 6.78 (2H, d, J = 9.0 Hz);

MS (EI) m/z: 334 [$M^+$], 278, 236.

(91b) 1-(4-isopropoxy phenyl)-1,4-diazepane

tert-butyl 4-(4-isopropoxy phenyl)-1,4-diazepane-1-carboxylate which was produced in Example 91 (91a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Slightly orange prism crystal (yield 89%)

Mp 62-64°C;

IR (film) $\nu_{max}$ 2974, 2932, 1511, 1237, 1114, 957, 815 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.29 (6H, d, J = 5.9 Hz), 1.88 (2H, quint, J = 5.9 Hz), 2.83 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.5 Hz), 3.49 (2H, t, J = 5.5 Hz), 3.52 (2H, t, J = 5.9 Hz), 4.35 (1H, sept, J = 5.9 Hz), 6.61 (2H, d, J = 9.0 Hz), 6.79 (2H, d, J = 9.0 Hz);

MS (EI) m/z: 234 [$M^+$], 191, 178.

(91c) 4-[4-(4-isopropoxyphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

1-(4-isopropoxy phenyl)-1,4-diazepane which was produced in Example 91 (91b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was

performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Slightly brown powder (yield 32%)

Mp 216-218°C;

IR (KBr) $\nu_{max}$ 3440, 3128, 3046, 2974, 2205, 1625, 1511, 1511, 1241 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.30 (6H, d, J = 5.9 Hz), 2.11 (2H, quint, J = 5.9 Hz), 3.51 (2H, t, J = 5.9 Hz), 3.73 (2H, t, J = 5.4 Hz), 3.76 (2H, t, J = 5.9 Hz), 4.12 (2H, t, J = 5.4 Hz), 4.39 (1H, sept, J = 5.9 Hz), 6.21 (1H, d, J = 7.8 Hz), 6.67 (2H, d, J = 8.8 Hz), 6.82 (2H, d, J = 8.8 Hz), 7.23 (1H, d, J = 7.8 Hz), 1184 (1H, bs);

MS (EI) m/z: 368 [$M^+$], 325, 148;

Anal. Calcd for $C_{20}H_{24}N_4OS \cdot 0.15H_2O$: C, 64.71; H, 6.60; N, 15.09; S, 8.64. Found: C, 64.59; H, 6.46; N, 15.09; S, 8.47.

(91d) 3-amino-4-[4-(4-isopropoxyphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-isopropoxyphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 91 (91c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly yellow powder 79%

Mp 173-175°C;

IR (KBr) $\nu_{max}$ 3441, 3324, 2973, 1644, 1579, 1510, 1370, 1235 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.21 (6H, d, J = 5.9 Hz), 2.07-2.16 (2H, m), 3.16-3.24 (2H, m), 3.25-3.33 (2H, m), 3.47 (2H, t, J = 5.9 Hz), 3.69 (2H, t, J = 4.7 Hz), 4.37 (1H, sept, J = 5.9 Hz), 6.68 (2H, d, J = 9.0 Hz), 6.76 (2H, d, J = 9.0 Hz), 6.97 (2H, bs), 7.03-7.11 (3H, m), 8.37 (1H, d, J = 5.5 Hz);

MS (EI) m/z: 425 [$M^+$], 382, 275, 183;

Anal. Calcd for $C_{22}H_{27}N_5O_2S$: C, 62.09; H, 6.40; N, 16.46; S, 7.54. Found: C, 61.83; H, 6.23; N, 16.32; S, 7.38.

(Example 92) 3-amino-4-[4-(4-tert-butylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-115)

(92a) tert-butyl 4-(4-tert-butylphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

White powder (yield 9%)

Mp 62-64°C;

IR (KBr) $\nu_{max}$ 2962, 1686, 1520, 1420, 1364, 1246, 1170 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.27 (9H, s), 1.35 (4.5H, s), 1.43 (4.5H, s), 1.91-2.00 (1H, m), 3.21 (1H, t, J = 6.3 Hz), 3.32 (1H, t, J = 5.9 Hz), 3.48-3.59 (6H, m), 6.62 (2H, d, J = 8.8 Hz), 7.20 (2H, d, J = 8.8 Hz);

MS (EI) m/z: 332 [$M^+$], 276, 261.

(92b) 1-(4-tert-butylphenyl)-1,4-diazepane

tert-butyl 4-(4-tert-butylphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 92 (92a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Pale brown oil (yield 97%)

IR (film) $\nu_{max}$ 2959, 1614, 1520, 1363, 1201, 812, 552 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.28 (9H, s), 1.89 (2H, quint, J = 5.9 Hz), 2.84 (2H, t, J = 5.9 Hz), 3.02 (2H, t, J = 5.5 Hz), 3.52 (2H, t, J = 5.5 Hz), 3.54 (2H, t, J = 5.9 Hz), 6.63 (2H, d, J = 8.4 Hz), 7.21 (2H, d, J = 8.4 Hz);

MS (EI) m/z: 232 [$M^+$], 217, 190, 176.

(92c) 4-[4-(4-tert-butylphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

1-(4-tert-butylphenyl)-1,4-diazepane which was produced in Example 92 (92b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Pale brown powder (yield 21%)

Mp 257-258°C;

IR (KBr) $\nu_{max}$ 3121, 3041, 2958, 2205, 1625, 1519, 1459, 1247 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.28 (9H, s), 2.12 (2H, quint, J = 5.9 Hz), 3.56 (2H, t, J = 5.9 Hz), 3.71-3.81 (4H, m), 4.13 (2H, t, J = 5.1 Hz), 6.20 (1H, d, J = 7.6 Hz), 6.66 (2H, d, J = 8.6 Hz), 7.22 (1H, d, J = 7.6 Hz), 7.24 (2H, d, J = 8.6 Hz), 11.94 (1H, bs);

MS (EI) m/z: 366 [$M^+$], 351, 188.

(92d) 3-amino-4-[4-(4-tert-butylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-tert-butylphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 92 (92c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly yellow powder (yield 72%)

Mp 231-232°C;

IR (KBr) $\nu_{max}$ 3440, 3324, 3182, 2957, 1645, 1579, 1579, 1519, 1364 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.21 (9H, s), 2.06-2.17 (2H, m), 3.22-3.16 (4H, m), 6.69 (2H, d, J = 9.0), 6.89 (2H, bs), 7.03-7.09 (3H, m), 7.17 (2H, d, J = 9.0 Hz), 8.38 (1H, d, J = 5.5 Hz);

MS (EI) m/z: 423 [$M^+$], 391, 275;

Anal. Calcd for $C_{23}H_{29}N_5OS \cdot 0.27H_2O$: C, 64.48; H, 6.95; N, 16.35; S, 7.48. Found: C, 64.17; H, 6.64; N, 16.31; S, 7.43.

(Example 93) 3-amino-4-[4-(4-ethylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-112)

(93a) tert-butyl 4-(4-ethylphenyl)-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Org.Lett.,4,581-584(2002) and the title compound was synthesized.

Colourless oil (yield 11%)

IR (film) $\nu_{max}$ 2964, 1695, 1519, 1415, 1236, 1169 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.19 (3H, t, J = 7.6 Hz), 1.37 (4.5H, s), 1.44 (4.5H, s), 1.92-2.01 (2H, m), 2.53 (2H, q, J = 7.6 Hz), 3.19 (1H, t, J = 6.3 Hz), 3.30 (1H, t, J = 5.9 Hz), 3.47-3.59 (6H, m), 6.62 (2H, d, J = 8.4 Hz), 7.02 (2H, d, J = 8.4 Hz);

MS (FAB) m/z: 304 [$M^+$], 248, 160.

(93b) 1-(4-ethylphenyl)-1,4-diazepane

tert-butyl 4-(4-ethylphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 93 (93a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Pale brown oil (yield 100%)

IR (film) $\nu_{max}$ 2929, 1616, 1519, 1189, 813 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.19 (3H, t, J = 7.6 Hz), 1.88 (2H, quint, J = 5.9 Hz), 2.54 (2H, q, J = 7.6 Hz), 2.82 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J - 5.5 Hz), 3.49-3.57 (2H, m), 6.62 (2H, d, J = 8.8 Hz), 7.03 (2H, d, J = 8.8 Hz);

MS (EI) m/z: 204 [$M^+$], 162, 148.

(93c) 4-[4-(4-ethylphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

1-(4-ethylphenyl)-1,4-diazepane which was produced in Example 93 (93b) was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Slightly brown powder (yield 22%)

Mp 226-229°C;

IR (KBr) $\nu_{max}$ 3122, 2959, 2205, 1625, 1517, 1457, 1246 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.20 (2H, t, J = 7.6 Hz), 2.11 (2H, quint, J = 5.9 Hz), 2.55 (2H, q, J = 7.6 Hz), 3.55 (2H, t, J = 5.9 Hz), 3.74 (2H, t, J = 5.9 Hz), 3.77 (2H, t, J = 5.1 Hz), 4.12 (2H, t, J = 5.1 Hz), 6.19 (1H, d, J = 7.6 Hz), 6.65 (2H, d, J = 8.6 Hz), 7.06 (2H, d, J = 8.6 Hz), 7.20 (1H, d, J = 7.6 Hz), 11.58 (1H, bs);

MS (EI) m/z: 338 [$M^+$], 323, 174, 160.

(93d) 3-amino-4-[4-(4-ethylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[4-(4-ethylphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 93 (93c) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile, and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

White powder (yield 82%)

Mp 186-188°C;

IR (KBr) $\nu_{max}$ 3439, 3324, 3178, 2958, 1643, 1579, 1518, 1369 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.14 (3H, t, J = 7.4 Hz), 2.07-2.17 (2H, m), 2.49 (2H, q, J = 7.4 Hz), 3.15-3.35 (4H, m), 3.53 (2H, t, J = 5.9 Hz), 3.74 (2H, t, J = 4.7 Hz), 6.70 (2H, d, J = 8.4 Hz), 6.96 (1H, bs), 7.02 (2H, d, J = 8.4 Hz), 7.04-7.14 (3H, m), 8.40 (1H, d, J = 5.5 Hz);

MS (EI) m/z: 395 [$M^+$], 377, 189;

Anal. Calcd for $C_{21}H_{25}N_5OS$: C, 63.77; H, 6.37; N, 17.71; S, 8.11. Found: C, 63.56; H, 6.25; N, 17.68; S, 8.10.

(Example 94) 4-[4-(4-acetylphenyl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-99)

(94a) tert-butyl 4-(4-acetylphenyl)-1,4-diazepane-1-carboxylate

4-fluoro acetophenone was used in place of 4-fluoronitrobenzene and the reaction was performed in a similar method as described in Example 59 (59a) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2974, 1596, 1523, 1416, 1363, 1284, 1237, 1191, 929, 819, 756 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.36 (4.5H, s), 1.42 (4.5H, s), 1.94-2.01 (2H, m), 2.50 (1H, s), 3.21 (1H, t, J = 5.9 Hz), 3.32 (1H, t, J = 5.9 Hz), 3.58-3.64 (6H, m), 6.66 (2H, d, J = 8.6 Hz), 7.83 (2H, t, J = 8.6 Hz);

HRMS m/z calcd for $C_{18}H_{26}O_3N_2$ 318.1944, found 318.1934;

MS (EI) m/z: 318 [$M^+$], 261, 247, 217, 188, 174, 162, 132, 105, 91, 57, 41.

(94b) 1-[4-(1,4-diazepan-1-yl)phenyl]ethanone

tert-butyl 4-(4-acetylphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 94 (94a) was used in place of tert-butyl 4-phenyl-1,4-diazepane-1-carboxylate and the reaction was performed in a similar method as described in Example 57 (57b) and the title compound was obtained.

Brown liquid

IR (KBr) $\nu_{max}$ 2931, 1658, 1597, 1523, 1403, 1360, 1285, 1191, 820 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.91 (2H, quint, J = 5.9 Hz), 2.50 (3H, s), 2.83 (2H, t, J = 5.9 Hz), 3.04 (2H, t, J = 5.4 Hz), 3.61 (2H, t, J = 5.4 Hz), 3.66 (2H, t, J = 6.4 Hz), 6.68 (2H, d, J = 8.8 Hz), 7.85 (2H, d, J = 8.8 Hz);

HRMS m/z calcd for $C_{13}H_{18}ON_2$ 218.1420.1313, found 218.1422;

MS (EI) m/z: 218 [$M^+$], 203, 176, 162, 148, 132, 70, 43.

(94c) (2Z)-3-[4-(4-acetylphenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide

1-[4-(1,4-diazepan-1-yl)phenyl]ethanone which was produced in Example 94 (94b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained.

Yellow powder

Mp 173-177°C;

IR (KBr) $\nu_{max}$ 3310, 3178, 2183, 1593, 1524, 1407, 1354, 1289, 1194, 825, 594 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.89-1.96 (2H, m), 2.23 (3H, s), 2.42 (3H, s), 3.49-3.54 (2H, m), 3.60-3.66 (4H, m), 3.83-3.86 (2H, m), 6.81 (2H, d, J = 9.0 Hz), 7.76 (2H, d, J = 9.0 Hz), 7.16 (2H, t, J = 7.3 Hz), 8.39 (1H, brs), 9.04 (1H, brs);

HRMS m/z calcd for $C_{18}H_{23}ON_4S$ 343.1592, found 343.1595;

MS (FAB) m/z: 343 $[M+H]^+$, 326, 273, 246, 219, 165, 120, 65;

Anal. Calcd for $C_{18}H_{22}N_4OS \cdot 0.40H_2O$: C, 61.83; H, 6.57; N, 16.02; S, 9.17. Found: C, 61.52; H, 6.35; N, 15.90, S, 9.52.

(94d) 4-[(4-acetylphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-3-[4-(4-acetylphenyl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 94 (94c) (504 mg, 1.47 mmol) and N,N-dimethylformamide dimethylacetal (175 mg, 1.47 mmol) were dissolved in N,N-dimethylformamide (2 mL) and the mixture was stirred at 60°C for 80 minutes. After 1N hydrochloric acid was added to make the reaction solution slightly acidic, ethyl acetate (10 mL) and water (20 mL) were added. The deposited solid was separated by filtration and the title compound was obtained (518 mg, 38%).

Pale brown powder

Mp 265-270°C;

IR (KBr) $\nu_{max}$ 2940, 2206, 1625, 1593, 1521, 1355, 1288, 1248, 1238, 1192, 1143, 929, 817 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.91-1.97 (2H, m), 2.42 (3H, s), 3.64 (2H, t, J = 5.9 Hz), 3.76 (2H, t, J = 5.9 Hz), 3.86 (2H, t, J = 5.4 Hz), 3.98 (2H, t, J = 5.4 Hz), 6.44 (1H, d, J = 7.8 Hz), 6.85 (1H, d, J = 8.8 Hz), 7.87 (1H, t, J = 7.8 Hz), 7.77 (2H, t, J = 8.8 Hz), 12.57 (1H, brs);

HRMS m/z calcd for $C_{19}H_{21}ON_4S$ 353.1436, found 353.1425;

MS (EI) m/z: 352 [$M^+$], 337, 323, 218, 204, 174, 162, 132, 105, 91, 77, 43;

Anal. Calcd for $C_{19}H_{20}N_4OS \cdot 0.33H_2O$: C, 63.66; H, 5.81; N, 15.63; S, 8.95. Found: C, 63.58; H, 5.80; N, 15.63, S, 8.74.

(94e) 4-[4-(4-acetylphenyl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide

4-[(4-acetylphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 94 (94d) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c), and the title compound was obtained.

Pale brown powder

Mp 279-282°C (decomposition);

IR (KBr) $\nu_{max}$ 3439, 3326, 3183, 1653, 1595, 1364, 1279, 1193, 939, 820 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.16-2.18 (2H, m), 2.44 (3H, s), 3.19-3.20 (2H, m), 3.30-3.32 (2H, m), 3.66 (2H, t, J = 6.3 Hz), 3.87 (2H, t, J = 4.9 Hz), 6.84 (2H, d, J = 8.8 Hz), 6.99 (2H, brs), 7.08 (1H, d, J = 5.4 Hz), 8.10 (2H, brs), 7.80 (2H, d, J = 8.8 Hz), 8.41 (1H, d, J = 5.4 Hz);

MS (EI) m/z: 409 [$M^+$].

(Example 95) 3-amino-4-[3-methyl-4-(3-methylphenyl)piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-77)

(95a) 4-[3-methyl-4-(3-methylphenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

2-methyl-1-(3-methylphenyl) piperazine was used in place of 1-(4-methylphenyl)-1,4-diazepane and the reaction was performed in a similar method as described in Example 77 (77c) and the title compound was obtained.

Pale brown powder (yield 23%)

Mp 250-251°C;

IR (KBr) $\nu_{max}$ 3122, 3039, 2970, 2208, 1621, 1496, 1447, 1248, 1011 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 0.99 (3H, d, J = 6.3 Hz), 2.25 (3H, s), 3.14-3.23 (1H, m), 3.37-3.52 (2H, m), 3.67 (1H, dd, J = 13.3, 3.5 Hz), 3.91-3.99 (1H, m), 4.01-4.15 82H, m), 6.53 (2H, d, J = 7.6 Hz), 6.58 (1H, d, J = 7.4 Hz), 6.65-6.71 (2H, m), 7.09 (1H, t, J = 7.4 Hz), 7.49 (1H, d, J = 7.6 Hz);

MS (FAB) m/z: 325 $[M+H]^+$, 200;

Anal. Calcd for $C_{18}H_{20}N_4S \cdot 0.32H_2O$: C, 65.47; H, 6.30; N, 16.97; S, 9.71. Found: C, 65.24; H, 6.38; N, 17.19; S, 9.78.

(95b) 3-amino-4-[3-methyl-4-(3-methylphenyl)piperazin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[3-methyl-4-(3-methylphenyl)piperazin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 95 (95a) was used in place of 4-(isobutylamino)-2-thioxo-1,2-dihydropyridine-3-carbonitrile and the reaction was performed in a similar method as described in Example 5 (5c) and the title compound was obtained.

Slightly brown powder (yield 81%)

Mp 215-217°C;

IR (KBr) $\nu_{max}$ 3449, 3325, 3179, 2972, 2836, 1644, 1580, 1501, 1370 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 0.99-1.14 (3H, m), 2.27 (3H, s), 2.62-3.51 (7H, m), 6.58-6.69 (1H, m), 6.74-6.85 (2H, m), 6.96 (2H, bs), 7.06-7.19 (4H, m), 8.46 (1H, d, J = 5.5 Hz);

MS (EI) m/z: 382 $[M+H]^+$, 200;

Anal. Calcd for $C_{20}H_{23}N_5OS \cdot 0.16$: C, 62.50; H, 6.12; N, 18.22; S, 8.34. Found: C, 62.49; H, 6.19; N, 18.15; S, 8.16.

(Example 96) 3-amino-4-(4-pyridin-3-yl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-140)

(96a) (2Z)-2-cyano-3-(4-pyridin-3-yl-1,4-diazepan-1-yl)but-2-enethioamide

1-pyridin-3-yl-1,4-diazepane (J. Med. Chem. (2000), 43, 2217-2226) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 83%.

Mp 162-164°C;

IR (KBr) $\nu_{max}$ 3300, 3164, 2187, 1583, 1530, 796, 707 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.91-1.97 (2H, m), 2.24 (3H, s), 3.51-3.63 (6H, m), 3.76-3.79 (2H, m), 7.11-7.15 (2H, m), 7.82-7.84 (1H, m), 8.14 (1H, brs), 8.35 (1H, br), 9.00 (1H, br);

MS (FAB) m/z: 302 $[M+H]^+$;

Anal. Calcd for $C_{15}H_{19}N_5S \cdot 0.1\ H_2O$: C, 59.42; H, 6.38; N, 23.10; S, 10.57. Found: C, 59.53; H, 6.48; N, 22.88; S, 10.57.

(96b) 3-amino-4-(4-pyridin-3-yl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-(4-pyridin-3-yl-1,4-diazepan-1-yl)but-2-enethioamide which was produced in Example 96 (96a) (485 mg, 1.61 mmol) and N,N-dimethylformamide dimethylacetal (211 mg, 1.77 mmol) were dissolved in N,N-dimethylformamide (3 mL) and the mixture was stirred at room temperature for one

hour. Furthermore, it was stirred from 100°C to 120°C for 1.5 hours. The reaction solution was cooled to room temperature and 8N aqueous solution of sodium hydroxide (0.3 mL) and 2-chloroacetamide (196 mg, 2.09 mmol) were added. Water (3 mL) was added after the mixture was stirred at room temperature for three hours. The deposited solid was separated by filtration and washed with water and ethanol and 239 mg of a solid was obtained. The obtained solid was recrystallized from ethanol (2 mL) and 195 mg of the title compound was obtained (yield 33%).
Mp 214-216°C;
IR (KBr) $\nu_{max}$ 3444, 3324, 3166, 1650, 1579, 1495, 1368, 794, 709 $cm^{-1}$;
$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.14-2.19 (2H, m), 3.16-3.22 (2H, m), 3.27-3.81 (2H, m), 3.55-3.58 (2H, m), 3.79-3.81 (2H, m), 6.97 (2H, brs), 7.07 (1H, d, J = 5.5 Hz), 7.09 (2H, brs), 7.10-7.16 (2H, m), 7.83 (1H, dd, J = 2.0, 4.3 Hz), 8.16 (1H, d, J = 2.0 Hz), 8.35 (1H, d, J = 5.5 Hz);
MS (FAB) m/z: 369 $[M+H]^+$.

(Example 97) 3-amino-4-[4-(1,3-thiazol-2-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-136)
(97a) 1-(1,3-thiazol-2-yl)-1,4-diazepane dihydrochloride

2-bromothiazole (8.20 g, 50 mmol) and homopiperazine (10.00 g, 100 mmol) were stirred in N-butanol (100 mL) under heat reflux for 24 hours. The reaction mixture was allowed to stand at room temperature for 24 hours and the deposited solid was separated by filtration. 1N aqueous solution of sodium hydroxide (30 mL) was added to the residue which was obtained by concentrating the filtrate under reduced pressure and the aqueous layer was extracted with methylene chloride (3x100 mL). The extract was concentrated after drying over sodium sulfate under reduced pressure. The residue was dissolved in methanol (30 mL) and 4N hydrochloric acid-1,4-dioxane solution (30 mL) was added. The deposited

hydrochloride was separated by filtration and washed with 1,4-dioxane and acetone and 9.43 g (yield 74%) of the title compound was obtained.

IR (neat) $\nu_{max}$ 1603, 1581, 743 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 2.13-2.19 (2H, m), 3.18-3.25 (2H, m), 3.30-3.36 (2H, m), 3.64-3.67 (2H, m), 3.96-3.99 (2H, m), 6.98 (1H, d, J = 3.9 Hz), 7.35 (1H, d, J = 3.9 Hz);

MS (EI) m/z: 183 [$M^+$], 83;

Anal. Calcd for $C_8H_{13}N_3S \cdot 2(HCl) \cdot 0.1(H_2O)$: C, 37.24; H, 5.94; N, 16.29; S, 12.43; Cl, 27.48. Found: C, 37.33; H, 5.88; N, 16.24; S, 12.37; Cl, 27.27.

(97b) 1-(1,3-thiazol-2-yl)-1,4-diazepane

After 1-(1,3-thiazol-2-yl)-1,4-diazepane dihydrochloride (5.11 g, 19.9 mmol) which was produced in Example 97 (97a) was mixed with 1N aqueous solution of sodium hydroxide (60 mL), the mixture was extracted with methylene chloride (3x50 mL). The extract was dried over sodium sulfate and concentrated under reduced pressure and 3.60 g (yield 99%) of the title compound was obtained.

IR (neat) $\nu_{max}$ 3304, 1534, 1139, 614 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.90-1.96 (2H, m), 2.89-2.91 (2H, m), 3.04-3.07 (2H, m), 3.66-3.70 (4H, m), 6.44 (1H, d, J = 3.5 Hz), 7.15 (1H, d, J = 3.5 Hz);

MS (EI) m/z: 183 [$M^+$], 83;

Anal. Calcd for $C_8H_{13}N_3S$: C, 52.43; H, 7.15; N, 22.93; S, 17.50. Found: C, 52.15; H, 7.46; N, 22.66; S, 10.50.

(97c) (2Z)-2-cyano-3-[4-(1,3-thiazol-2-yl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(1,3-thiazol-2-yl)-1,4-diazepane which was produced in Example 97 (97b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained (4.56 g). Yield 91%.

Mp 149-152°C;

IR (KBr) $\nu_{max}$ 3276, 3130, 2182, 1531, 885, 615 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.95-2.00 (2H, m), 2.27 (3H, s), 3.57-3.69 (6H, m), 3.80-3.84 (2H, m), 6.77 (1H, d, J = 3.5 Hz), 7.12 (1H, d, J = 3.5 Hz), 8.42 (1H, br), 9.06 (1H, br);

MS (FAB) m/z: 308 $[M+H]^+$;

Anal. Calcd for $C_{13}H_{17}N_5S_2$: C, 50.79; H, 5.57; N, 22.78; S, 20.86. Found: C, 50.52; H, 5.64; N, 22.44; S, 21.10.

(97d) 3-amino-4-[4-(1,3-thiazol-2-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-[4-(1,3-thiazol-2-yl)-1,4-diazepan-1-yl]but-2-enethioamide (394 mg, 1.28 mmol) which was produced in Example 97 (97c) and N,N-dimethylformamide dimethylacetal (168 mg, 1.41 mmol) were dissolved in N,N-dimethylformamide (2 mL) and the mixture was stirred at room temperature for one hour. Furthermore, it was stirred at 100°C for one hour. The reaction solution was cooled to room temperature and 8N aqueous solution of sodium hydroxide (0.3 mL) and 2-chloroacetamide (156 mg, 1.66 mmol) were added. Water (2 mL) was added after the mixture was stirred at room temperature overnight. The deposited solid was separated by filtration and 215 mg of a solid was obtained. The obtained solid was recrystallized from 95% ethanol (15 mL) and 150 mg of the title compound was obtained (yield 31%).

Mp 243-245°C;

IR (KBr) $\nu_{max}$ 3432, 3310, 3154, 1648, 1580, 1509, 1375, 933, 614 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.48-2.50 (2H, m), 3.19-3.37 (4H, m), 3.62 (2H, t, J = 5 9 Hz), 3.93-3.95 (2H, m), 6.73 (1H, d, J = 3.5 Hz), 7.00 (2H, brs), 7.06 (1H, d, J = 5.5 Hz), 7.10 (2H, brs), 7.13 (1H, d, J = 3.5 Hz), 8.39 (1H, d, J = 3.5 Hz);

MS (EI) m/z: 374 $[M^+]$;

Anal. Calcd for $C_{16}H_{18}N_6OS_2 \cdot 1.1\ H_2O$: C, 48.74; H, 5.16; N, 21.31; S, 16.26. Found: C, 48.98; H, 5.03; N, 21.22; S, 15.89.

(Example 98) 3-amino-4-[4-(6-methoxypyridin-3-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-144)

(98a) (2Z)-2-cyano-3-[4-(6-methoxypyridin-3-yl)-1,4-diazepan-1-yl]but-2-enethioamide

1-(6-methoxypyridin-3-yl)-1,4-diazepane (J. Med.Chem. (2000), 43,2217-2226) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 66%.

Mp 159-161°C;

IR (KBr) $\nu_{max}$ 3306, 3186, 2187, 1643, 1530, 1504, 1041 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.90-1.97 (2H, m), 2.25 (3H, s), 3.44-3.45 (4H, m), 3.60-3.68 (4H, m), 3.74 (3H, s), 6.66 (1H, d, J = 9.0 Hz), 7.28 (1H, dd, J = 3.1, 9.0 Hz), 7.67 (1H, d, J = 3.1 Hz), 8.31 (1H, br), 8.97 (1H, br);

MS (EI) m/z: 331 [$M^+$];

Anal. Calcd for $C_{16}H_{21}N_5SO \cdot 0.1\ H_2O$: C, 57.67; H, 6.41; N, 21.02; S, 9.62. Found: C, 57.74; H, 6.50; N, 20.84; S, 9.49.

(98b) 3-amino-4-[4-(6-methoxypyridin-3-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-[4-(6-methoxypyridin-3-yl)-1,4-diazepan-1-yl]but-2-enethioamide which was produced in Example 98 (98a) (220 mg, 0.66 mmol) and N,N-dimethylformamide dimethylacetal (83 mg, 0.70 mmol) were dissolved in N,N-dimethylformamide (2 mL) and the mixture was stirred at room temperature for two hours. Furthermore, it was stirred at 100°C for one hour. The reaction solution was cooled to room temperature and 8N aqueous solution of sodium hydroxide (0.2

mL) and 2-chloroacetamide (80 mg, 0.86 mmol) were added. The mixture was partitioned with water (50 mL) and ethyl acetate (50 mL) after stirring at room temperature for one hour. The organic layer was washed with a saturated saline solution (30 mL) and the solvent was evaporated under reduced pressure after drying over sodium sulfate. The residue was purified by silica gel chromatography (100% ethyl acetate) and was recrystallized from ethanol and 96 mg of the title compound was obtained (yield 36%).

Mp 170-172°C;

IR (KBr) $\nu_{max}$ 3440, 3323, 3183, 1645, 1579, 1499, 1370, 1033, 939, 819 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.10-2.16 (2H, m), 3.17-3.31 (4H, m), 3.49-3.52 (2H, m), 3.70-3.72 (2H, m), 3.75 (3H, s), 6.67 (1H, d, J = 9.0 Hz), 6.98 (2H, br), 7.06 (1H, d, J = 5.5 Hz), 7.07 (2H, br), 7.27 (1H, dd, J = 3.1, 9.0 Hz), 7.67 (1H, d, J = 3.1 Hz), 8.38 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 399 $[M+H]^+$;

Anal. Calcd for $C_{19}H_{22}N_6SO_2 \cdot 0.4\ H_2O$: C, 56.25; H, 5.66; N, 20.72; S, 7.90. Found: C, 55.97; H, 5.44; N, 21.11; S, 7.86.

(Example 99) 3-amino-4-(4-pyridin-2-yl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-139)

(99a) tert-butyl 2-pyridin-2-yl-1,4-diazepane-1-carboxylate

Synthesis was performed with reference to a method described in J. Org. Chem. (2001), 66, 7729-7737 as follows. Potassium tert-butoxide (1.68 g, 15 mmol), tris(dibenzylideneacetone)dipalladium (0 valent) (92 mg, 0.1 mmol), 1,3-bis(2,6-diisopropylphenyl)glyoxalin-2-ylidene) hydrochloride (85 mg, 0.2 mmol) were mixed in 1,4-dioxane (20 mL), and the mixture was added dropwise to 1,4-dioxane (10 mL) solution of 2-bromopyridine (2.37 g, 15 mmol) and N-Boc-homopiperazine (2.00 g, 10 mmol). After stirring at room temperature for 12 hours,

water (100 mL) and ethyl acetate (100 mL) were added to the reaction mixture and insolubles were removed with Celite. After the liquid was partitioned into the organic layer and aqueous layer, the organic layer was washed with a saturated saline solution (50 mL) and dried over sodium sulfate. The residue which was obtained by evaporating the solvent under reduced pressure was purified by silica gel column chromatography (hexane/ethyl acetate =4:1) and 2.27 g of the title compound was obtained (yield 82%).

IR (neat) $\nu_{max}$ 1694, 1597, 1494, 1240, 1169, 928, 770 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.38, (4.5H, s), 1.43, (4.5H, s), 1.92-1.99 (2H, m), 3.21-3.34 (2H, m), 3.54-3.78 (6H, m), 6.47-6.52 (2H, m), 7.38-7.42 (1H, m), 8.10-8.12 (1H, m);

MS (FAB) m/z: 278 $[M+H]^+$.

(99b) 1-pyridin-2-yl-1,4-diazepane

tert-butyl 2-pyridin-2-yl-1,4-diazepane-1-carboxylate (2.17 g, 7.8 mmol) which was produced in Example 99 (99a) was dissolved in methylene chloride (8 mL) and trifluoroacetic acid (8 mL) was added under ice-cooling. The reaction mixture was concentrated under reduced pressure after stirring at room temperature for three hours. 1N aqueous solution of sodium hydroxide (30 mL) was added to the residue and the aqueous layer was extracted with methylene chloride (3x40 mL). The extract was dried over sodium sulfate and the solvent was evaporated under reduced pressure and 1.34 g (yield 97%) of the title compound was obtained as oil.

IR (neat) $\nu_{max}$ 3308, 1597, 1496, 1440, 769 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 1.86-1.92 (2H, m), 2.83-2.86 (2H, m), 3.01-3.04 (2H, m), 3.69-3.74 (4H, m), 6.46-6.50 (2H, m), 7.40 (1H, ddd, J = 2.0, 7.1, 8.6 Hz), 8.12 (1H, ddd, J = 0.8, 2.0, 5.1 Hz);

MS (EI) m/z: 177 $[M^+]$, 121.

(99c) (2Z)-2-cyano-3-(4-pyridin-2-yl-1,4-diazepan-1-yl)but-2-enethioamide

1-pyridin-2-yl-1,4-diazepane which was produced in Example 99 (99b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 79%.

Mp 155-157°C;

IR (KBr) $\nu_{max}$ 3398, 3288, 3184, 2185, 1598, 1540, 1494, 1439, 773 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.88-1.94 (2H, m), 2.24 (3H, s), 3.55-3.70 (6H, m), 3.89-3.92 (2H, m), 6.57 (1H, dd, J = 5.0, 7.0 Hz), 6.72 (1H, d, J = 8.6 Hz), 7.50 (1H, ddd, J = 2.0, 7.0, 8.6 Hz), 8.07 (1H, dd, J = 2.0, 5.0 Hz), 8.34 (1H, br), 9.01 (1H, br);

MS (FAB) m/z: 302 $[M+H]^+$.

(99d) 4-(4-pyridin-2-yl-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-(4-pyridin-2-yl-1,4-diazepan-1-yl)but-2-enethioamide (0.90 g, 3.0 mmol) which was produced in Example 99 (99c) and N,N-dimethylformamide dimethylacetal (0.39 g, 3.3 mmol) were dissolved in N,N-dimethylformamide (5 mL) and the mixture was stirred at room temperature for one hour and further at 100°C for one hour. The reaction solution was cooled to room temperature and partitioned with isopropyl ether (20 mL) and 1N aqueous solution of sodium hydroxide (10 mL). The aqueous layer was made acidic (pH =4) with 1N hydrochloric acid and was neutralized by adding a saturated sodium bicarbonate aqueous solution. The deposited crystal was separated by filtration and washed with water and ethanol and a crude product of the title compound (0.37 g) was obtained.

Mp 220-224°C;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.88-1.94 (2H, m), 3.63-3.66 (2H, m), 3.76-3.79 (2H, m), 3.88-3.98 (4H, m), 6.41 (1H, d, J = 7.8 Hz), 6.53 (1H, dd, J = 5.0, 7.0 Hz), 6.71 (1H, d, J = 8.6 Hz), 7.81-7.35 (1H, m), 7.46 (1H, ddd, J = 2.0, 7.0, 8.6 Hz), 8.03 (1H, dd, J = 2.0, 5.0 Hz), 12.50 (1H, br).

(99e) 3-amino-4-(4-pyridin-2-yl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

A crude product (0.37 g) of 4-(4-pyridin-2-yl-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 99 (99d) was dissolved in N,N-dimethylformamide (4 mL) and 8N aqueous solution of sodium hydroxide (0.4 mL) and 2-chloroacetamide (0.14 g, 1.5 mmol) were added. Water (4 mL) was added after the mixture was stirred at room temperature for one hour. The deposited solid was separated by filtration and washed with water and ethanol and 0.33 g of a solid was obtained. The obtained solid was heated in 80% ethanol (5 mL) and the mixture was stirred, and after it was cooled, the solid was separated by filtration and 0.30 g of the title compound was obtained. Yield 27% from (2Z)-2-cyano-3-(4-pyridin-2-yl-1,4-diazepan-1-yl)but-2-enethioamide.

Mp 237-239°C;

IR (KBr) $\nu_{max}$ 3444, 3325, 3167, 1650, 1596, 1496, 1371, 942, 770 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.11-2.17 (2H, m), 3.17-3.32 (4H, m), 3.70 (2H, t, J = 6.3 Hz), 3.96-4.03 (2H, m), 6.57 (1H, dd, J = 5.1, 7.0 Hz), 6.69 (1H, d, J = 8.6 Hz), 7.01 (2H, brs), 7.07 (1H, d, J = 5.1 Hz), 7.10 (2H, brs), 7.51 (1H, ddd, J = 2.0, 7.0, 8.6 Hz), 8.09 (1H, dd, J = 2.0, 5.1 Hz), 8.39 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 369 $[M+H]^+$;

Anal. Calcd for $C_{18}H_{20}N_6SO \cdot 0.3\ H_2O$: C, 57.83; H, 5.55; N, 22.48; S, 8.58. Found: C, 57.99; H, 5.35; N, 22.43; S, 8.59.

(Example 100) 3-amino-4-(4-pyridin-4-yl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-141)

(100a) tert-butyl 4-pyridin-4-yl-1,4-diazepane-1-carboxylate

4-bromopyridine hydrochloride was used in place of 2-bromopyridine with 2.1 equivalent of potassium tert-butoxide, and the reaction was performed in a

similar method as described in Example 99 (99a). The residual substance which was obtained by post-treatment of the reaction was purified by silica gel column chromatography (Chromatorex NH, Fuji Silysia) (100% ethyl acetate) and the title compound was obtained. Yield 34%.

Mp 124-129°C;

IR (KBr) $\nu_{max}$ 1674, 1597, 1167, 987 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.36 (4.5H, s), 1.42 (4.5H, s), 1.92-1.99 (2H, m), 3.21-3.34 (2H, m), 3.52-3.59 (4H, m), 6.50 (2H, brd, J = 6.5 Hz), 8.18-8.20 (2H, m);

MS (EI) m/z: 277 $[M^+]$, 220;

Anal. Calcd for $C_{15}H_{23}N_3O_2$: C, 64.95; H, 8.36; N, 15.15. Found: C, 64.78; H, 8.46; N, 15.03.

(100b) Pyridin-4-yl-1,4-diazepane

tert-butyl 4-pyridin-4-yl-1,4-diazepane-1-carboxylate (0.42 g, 1.5 mmol) which was produced in Example 100 (100a) was dissolved in methanol (3 mL) and 1,4-4N hydrochloric acid -dioxane solution (3 mL) was added. The reaction mixture was concentrated under reduced pressure after stirring at room temperature for two hours. 1N aqueous solution of sodium hydroxide (10 mL) was added to the residue and the aqueous layer was extracted with methylene chloride (3x20 mL). The extract was dried over sodium sulfate and the solvent was evaporated under reduced pressure and 0.26 g (yield 97%) of the title compound was obtained as oil.

IR (neat) $\nu_{max}$ 3270, 1600, 1518, 804 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.86-1.92 (2H, m), 2.83 (2H, t, J = 5.9 Hz), 3.02 (2H, t, J = 5.3 Hz), 3.53-3.61 (4H, m), 6.51 (2H, d, J = 6.6 Hz), 8.20 (2H, d, J = 6.6 Hz);

MS (FAB) m/z: 178 $[M+H]^+$.

(100c) (2Z)-2-cyano-3-(4-pyridin-4-yl-1,4-diazepan-1-yl)but-2-enethioamide

Pyridin-4-yl-1,4-diazepane which was produced in Example 100 (100b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 57%.
Amorphous solid
IR (KBr) $\nu_{max}$ 3172, 2185, 1600, 1538, 1520, 1411 $cm^{-1}$;
$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.89-1.94 (2H, m), 2.23 (3H, s), 3.52-3.62 (6H, m), 3.78-3.80 (2H, m), 6.70 (2H, d, J = 6.7 Hz), 8.09 (2H, d, J = 6.7 Hz), 8.41 (1H, br), 9.04 (1H, br);
MS (FAB) m/z: 302 $[M+H]^+$.
(100d) 3-amino-4-(4-pyridin-4-yl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-(4-pyridin-4-yl-1,4-diazepan-1-yl)but-2-enethioamide which was produced in Example 100 (100c) (200 mg, 0.66 mmol) and N,N-dimethylformamide dimethylacetal (87 mg, 0.73 mmol) were dissolved in N,N-dimethylformamide (3 mL) and after stirring at room temperature for two hours, further stirred at 100°C for one hour. The reaction solution was cooled to room temperature and 8N aqueous solution of sodium hydroxide (0.2 mL) and 2-chloroacetamide (93 mg, 0.99 mmol) were added. Water (4 mL) was added after the mixture was stirred at room temperature for one hour. The deposited solid was separated by filtration after allowing to stand at room temperature for 15 hours and washed with water and then dried, and 55 mg of a crude product was obtained. The crude product was suspended in 80% aqueous ethanol (3 mL), and heated and the mixture was stirred and after it was cooled, the solid was separated by filtration and purified and 30 mg of the title compound was obtained (yield 12%).
Mp 288-291°C (decomposition);
IR (KBr) $\nu_{max}$ 3334, 1650, 1597, 1573, 1510, 1367 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 2.13-2.18 (2H, m), 3.15-3.30 (4H, m), 3.56-3.59 (2H, m), 3.79-3.81 (2H, m), 6.68 (2H, d, J = 6.7 Hz), 6.98 (2H, br), 7.06 (1H, d, J = 5.1 Hz), 7.09 (2H, br), 8.09 (2H, d, J = 6.7 Hz), 8.38 (1H, d, J = 5.1 Hz);
MS (EI) m/z: 368 [$M^+$], 108;
Anal. Calcd for $C_{18}H_{20}N_6OS \cdot 0.3\ H_2O$: C, 57.83; H, 5.55; N, 22.48; S, 8.58. Found: C, 57.76; H, 5.48; N, 22.46; S, 8.50.

(Example 101)
3-amino-4-[3-(methoxymethyl) piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-21)
(101a) tert-butyl 3-(methoxymethyl)piperidine-1-carboxylate

Sodium hydride (55% oily, 0.26 g, 6 mmol) was suspended in tetrahydrofuran (5 mL) and N,N-dimethylformamide (3 mL) solution of tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate (Bioorg.Med.Chem.Lett. 8, (1998), 1595-1600) (1.08 g, 5 mmol) was added, and further methyl iodide (0.85 g, 6 mmol) was added. Water (50 mL) was added to the reaction mixture after stirring at room temperature for three days, the aqueous layer was extracted with ethyl acetate (50 mL). The extract was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate =10:1) and 1.03 g of the title compound was obtained (yield 90%).
IR (neat) $\nu_{max}$ 1696, 1422, 1151 $cm^{-1}$;
$^1$H NMR ($CDCl_3$, 400MHz) δ 1.16-1.51 (2H, m), 1.46 (9H, s), 1.60-1.82 (3H, m), 2.64 (1H, br), 2.82 (1H, brt, J = 13.3 Hz), 3.24 (2H, d, J = 5.9 Hz), 3.32 (3H, s), 3.87 (1H, dt, J = 4.0, 13.3 Hz), 3.94 (1H, m);
MS (EI) m/z: 229 [$M^+$], 114;

Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.90; H, 9.77; N, 6.04.

(101b) 3-(methoxymethyl)piperidine

tert-butyl 3-(methoxymethyl)piperidine-1-carboxylate (1.03 g, 4.5 mmol) which was produced in Example 101 (101a) was dissolved in methylene chloride (4 mL) and trifluoroacetic acid (2 mL) was added under ice-cooling. The reaction mixture was concentrated under reduced pressure after stirring at room temperature for two hours. 1N aqueous solution of sodium hydroxide (20 mL) was added to the residue and the aqueous layer was extracted with methylene chloride (3x30 mL). The extract was dried over sodium sulfate and the solvent was evaporated under reduced pressure and 0.50 g of the title compound was obtained (yield 86%) as oil.

IR (neat) $\nu_{max}$ 3312, 1467, 1450, 1270, 1128, 1097 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 1.06-1.16 (1H, m), 1.40-1.51 (1H, m), 1.63-1.80 (3H, m), 2.33 (1H, t, J = 11.7 Hz), 2.55 (1H, dt, J = 2.7, 11.7 Hz), 3.00 (1H, brd, J = 12.1 Hz), 3.11 (1H, brd, J = 12.1 Hz), 3.20 (2H, d, J = 6.3 Hz), 3.31 (3H, s);

MS (EI) m/z: 129 [$M^+$], 114.

(101c) (2Z)-2-cyano-3-[3-(methoxymethyl)piperidin-1-yl]but-2-enethioamide

3-(methoxymethyl)piperidine which was produced in Example 101 (101b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 81%.

Mp 151-152°C;

IR (KBr) $\nu_{max}$ 3380, 3255, 3157, 2183, 1605, 1531, 1410, 1261 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.25-1.35 (1H, m), 1.48-1.59 (1H, m), 1.66-1.76 (2H, m), 1.85-1.94 (1H, m), 2.26 (3H, s), 2.91-2.97 (1H, m), 3.03-3.10 (1H, m), 3.16-3.24 (2H, m), 3.22 (3H, s), 3.50-3.63 (2H, d, J = 6.3 Hz), 8.18 (1H, br), 8.90 (1H, br);

MS (EI) m/z: 253 [$M^+$], 220;

Anal. Calcd for $C_{12}H_{19}N_3OS \cdot 0.1\ H_2O$: C, 56.49; H, 7.58; N, 16.47; S, 12.57. Found: C, 56.62; H, 7.41; N, 16.39; S, 12.60.

(101d) 4-[3-(methoxymethyl)piperidin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-[3-(methoxymethyl)piperidin-1-yl]but-2-enethioamide which was produced in Example 101 (101c) (0.39 g, 1.5 mmol) and N,N-dimethylformamide dimethylacetal (0.20 g, 1.7 mmol) were dissolved in N,N-dimethylformamide (3 mL) and the mixture was stirred at room temperature for one hour, and further stirred at 100°C for one hour. The reaction solution was cooled to room temperature and water (50 mL) was added. The aqueous layer was extracted with ethyl acetate (3x50 mL) and dried over sodium sulfate and the extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol =20:1) and 125 mg of the title compound was obtained (yield 31%).

Mp 154-156°C;

IR (KBr) $\nu_{max}$ 2208, 1622, 1550, 1517, 1249 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.26-1.93 (5H, m), 3.04 (1H, dd, J = 10.2, 13.3 Hz), 3.18-3.27 (3H, m), 3.24 (3H, s), 3.96-4.02 (2H, m), 6.46 (1H, d, J = 7.8 Hz), 7.46 (1H, d, J = 7.8 Hz);

MS (EI) m/z: 263 [$M^+$], 248, 218;

Anal. Calcd for $C_{13}H_{17}N_3OS \cdot 0.1\ H_2O$: C, 58.89; H, 6.54; N, 15.85; S, 12.09. Found: C, 58.93; H, 6.60; N, 16.00; S, 12.07.

(101e) 3-amino-4-[3-(methoxymethyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[3-(methoxymethyl) piperidin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile (120 mg, 0.46 mmol) which was produced in Example 101 (101d) was

dissolved in N,N-dimethylformamide (1 mL) and 8N aqueous solution of sodium hydroxide (0.2 mL) and 2-chloroacetamide (55 mg, 0.59 mmol) were added. The mixture was blended with water (50 mL) and ethyl acetate (50 mL) and partitioned after stirring at room temperature for one hour. After the organic layer was washed with a saturated saline solution (30 mL), it was dried over sodium sulfate and concentrated under reduced pressure. Ether was added to the residue and solidified, and the deposited solid was separated by filtration and further washed with ether and 138 mg of the title compound was obtained (yield 95%).

Mp 229-230°C;

IR (KBr) $\nu_{max}$ 3432, 3320, 3144, 1653, 1577, 1501, 1375, 1097 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.03-1.15 (1H, m), 1.73-1.84 (3H, m), 2.07-2.19 (1H, m), 2.35-3.44 (4H, m), 3.22 (3H, s), 6.97 (2H, br), 7.00 (1H, d, J = 5.1 Hz), 7.09 (2H, br), 8.40 (1H, d, J = 5.1 Hz);

MS (EI) m/z: 320 [$M^+$];

Anal. Calcd for $C_{15}H_{20}N_4O_2S$: C, 56.23; H, 6.29; N, 17.49; S, 10.01. Found: C, 56.21; H, 6.45; N, 17.37; S, 9.80.

(Example 102) 3-amino-4-(1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide dihydrochloride (Exemplified Compound No. 3-78)

3-amino-4-(4-tert-butoxycarbonyl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (0.77 g, 2.0 mmol) which was produced in Example 55 (55c) was dissolved in 1,4-dioxane (4 mL) and 4N hydrochloric acid/1,4-dioxane (4 mL) was added. The reaction mixture was concentrated under reduced pressure after stirring at room temperature for four hours and the 0.72 g of the title compound was obtained.

Mp >295°C;

IR (KBr) $\nu_{max}$ 3457, 3371, 3291, 1654, 1614, 1579 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 2.12-2.19 (2H, m), 3.20-3.26 (2H, m), 3.36-3.42 (2H, m), 3.58-3.64 (2H, m), 3.80-3.87 (2H, m), 7.11 (1H, d, J = 6.5 Hz), 7.27 (2H, br), 8.44 (1H, d, J = 6.5 Hz), 9.46 (2H, br);

MS (FAB) m/z: 292 $[M+H]^+$;

Anal. Calcd for $C_{13}H_{17}N_5OS \cdot 2(HCl) \cdot 0.3\ H_2O$: C, 42.24; H, 5.34; N, 18.94; S, 8.67; Cl, 19.18. Found: C, 42.39; H, 5.22; N, 19.01; S, 8.53; Cl, 18.93.

(Example 103) 4-(4-acetyl-1,4-diazepan-1-yl)-3-aminothieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-149)

3-amino-4-(1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide dihydrochloride (182 mg, 0.5 mmol) which was produced in Example 102 was suspended in tetrahydrofuran (3 mL) and blended with triethylamine (0.15 mL) and acetic acid anhydride (77 mg, 0.75 mmol) and the mixture was stirred at room temperature for two hours. A saturated sodium bicarbonate aqueous solution (20 mL) was added to the reaction mixture and the aqueous layer was extracted with methylene chloride (2x30 mL). After having dried in sodium sulfate in extract, the solvent was evaporated under reduced pressure and 55 mg of the title compound (yield 33%) was obtained when the obtained solid was recrystallized from ethanol (4 mL).

Mp 214-215°C;

IR (KBr) $\nu_{max}$ 3425, 3333, 3188, 1632, 1581, 1370, 938 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.97-2.08 (2H, m), 2.02 (1.5H, s), 2.05 (1.5H, s), 3.15-3.24 (4H, m), 3.55-3.62 (2H, m), 3.69-3.77 (2H, m), 7.01 (2H, br), 7.04 (0.5H, d, J = 5.5 Hz), 7.07 (0.5H, d, J = 5.5 Hz), 7.09 (2H, br), 8.38 (0.5H, d, J = 5.5 Hz),8.41 (0.5H, d, J = 5.5 Hz);

MS (FAB) m/z: 334 $[M+H]^+$;

Anal. Calcd for $C_{15}H_{19}N_5O_2S \cdot 0.1\ H_2O$: C, 53.75; H, 5.77; N, 20.89; S, 9.57. Found: C, 53.89; H, 5.75; N, 20.73; S, 9.42.

(Example 104) 3-amino-4-[4-(methylsulfonyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-151)

3-amino-4-(1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide dihydrochloride which was produced in Example 102 (182 mg, 0.5 mmol) and potassium carbonate (221 mg, 1.6 mmol) were suspended in tetrahydrofuran (5 mL), and the resultant solution was blended with methanesulfon acid anhydride (105 mg, 0.6 mmol) and the mixture was stirred at room temperature for 15 hours. Water (20 mL) and ethyl acetate (30 mL) were added to the reaction mixture and partitioned and the aqueous layer was extracted with ethyl acetate (30 mL). After the combined organic layer was dried over sodium sulfate, the solvent was evaporated under reduced pressure and 72 mg of the title compound (yield 39%) was obtained when the obtained residue was purified by silica gel column chromatography (methylene chloride/methanol = 15:1).

Mp 214-217°C;

IR (KBr) $\nu_{max}$ 3424, 3327, 3155, 1650, 1582, 1371, 1323, 1147, 934 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.02-2.07 (2H, m), 2.96 (3H, s), 3.26-3.84 (2H, m), 3.44-3.47 (2H, m), 3.58-3.61 (2H, m), 7.04 (2H, br), 7.10 (1H, d, J = 5.5 Hz), 7.01 (2H, br), 8.44 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 370 $[M+H]^+$;

Anal. Calcd for $C_{14}H_{19}N_5O_3S_2$: C, 45.51; H, 5.18; N, 18.96; S, 17.36. Found: C, 45.38; H, 5.08; N, 18.64; S, 17.04.

(Example 105) 3-amino-4-[4-(6-chloropyridazin-3-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-148)

(105a) (2Z)-3-[4-(6-chloropyridazin-3-yl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide

1-(6-chloropyridazin-3-yl)-1,4-diazepane (J. Med. Chem. (2002), 45,4011-4017) was used in place of isobutylamine; and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 60%.

Amorphous solid

IR (KBr) $\nu_{max}$ 3289, 3185, 2191, 1587, 1531, 1453, 1429 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.89-1.95 (2H, m), 2.25 (3H, s), 3.59-3.66 (4H, m), 3.74-3.77 (2H, m), 3.97-4.00 (2H, m), 7.31 (1H, d, J = 9.8 Hz), 7.51 (1H, d, J = 9.8 Hz), 8.40 (1H, br), 9.04 (1H, br);

MS (FAB) m/z: 337 $[M+H]^+$.

(105b) 3-amino-4-[4-(6-chloropyridazin-3-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-3-[4-(6-chloropyridazin-3-yl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide (0.75 g, 2.2 mmol) which was produced in Example 105 (105a) and N,N-dimethylformamide dimethylacetal (0.28 g, 2.3 mmol) were dissolved in N,N-dimethylformamide (5 mL) and the mixture was stirred at room temperature for one hour, and further stirred at 100°C for two hours. The reaction solution was cooled to room temperature and 8N aqueous solution of sodium hydroxide (0.5 mL) and 2-chloroacetamide (0.27 g, 2.9 mmol) were added. Water (30 mL) was added after the mixture was stirred at room temperature for one hour. The aqueous layer was extracted with ethyl acetate (2x50 mL) and the extract was concentrated after drying over sodium sulfate under reduced pressure. The obtained residue was purified by silica gel column chromatography (methylene chloride/methanol =20:1) and the obtained crystal was further washed with ethanol and 0.15 g of the title compound was obtained (yield 17%).

Mp 232-234°C;

IR (KBr) $\nu_{max}$ 3320, 1645, 1584, 1501, 1450, 1372, 939 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.13-2.19 (2H, m), 3.18-3.23 (2H, m), 3.30-3.35 (2H, m), 3.75-3.78 (2H, m), 4.00-4.05 (2H, m), 7.00 (2H, br), 7.05 (1H, d, J = 5.1 Hz), 7.09 (2H, br), 7.26 (1H, d, J = 9.6 Hz), 7.50 (1H, d, J = 9.6 Hz), 8.38 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 404 $[M+H]^+$;

Anal. Calcd for $C_{17}H_{18}N_7OSCl \cdot 0.3\ H_2O$: C, 49.89; H, 4.58; N, 23.95; S, 7.83; Cl, 8.66. Found: C, 49.93; H, 4.52; N, 23.93; S, 8.09; Cl, 8.39.

(Example 106) 3-amino-4-[4-(5-methylpyridin-2-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-143)

(106a) tert-butyl 4-(5-methylpyridin-2-yl)-1,4-diazepane-1-carboxylate

2-bromo-5-methylpyridine was used in place of 2-bromopyridine and the reaction was performed in a similar method as described in Example 99 (99a). The obtained crude product was purified by silica gel column chromatography (hexane/ethyl acetate =5:1) and the title compound was obtained at yield 81%.

IR (neat) $\nu_{max}$ 1694, 1612, 1503, 1415, 1170, 929 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.39 (4.5H, s), 1.44 (4.5H, s), 1.92-1.98 (2H, m), 2.19 (3H, s), 3.20-3.33 (2H, m), 3.54-3.76 (6H, m), 6.45 (1H, d, J = 8.6 Hz), 7.26 (1H, dd, J = 2.0, 8.6 Hz), 7.96 (1H, d, J = 2.0 Hz);

MS (EI) m/z: 291 $[M^+]$, 135;

Anal. Calcd for $C_{16}H_{25}N_3O_2 \cdot 0.4\ H_2O$: C, 64.36; H, 8.71; N, 14.07. Found: C, 64.35; H, 8.96; N, 13.98.

(106b) 1-(5-methylpyridin-2-yl)-1,4-diazepane

The reaction was performed in a similar method as described in Example 100 (100b) and the title compound was obtained at yield 97%.

IR (neat) $\nu_{max}$ 3307, 1613, 1503, 1409, 804 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.85-1.91 (2H, m), 2.17 (3H, s), 2.82-2.85 (2H, m), 3.01-3.03 (2H, m), 3.68-3.72 (4H, m), 6.43 (1H, d, J = 8.6 Hz), 7.26 (1H, dd, J = 2.0, 8.6 Hz), 7.97 (1H, d, J = 2.0 Hz);

MS (FAB) m/z: 192 $[M+H]^+$, 135.

(106c) (2Z)-2-cyano-3-[(4-(5-methylpyridin-2-yl)-1,4-diazepan-1-yl)but-2-enethioamide

1-(5-methylpyridin-2-yl)-1,4-diazepane which was produced in Example 106 (106b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 79%.

Mp 140-145°C;

IR (KBr) $\nu_{max}$ 3274, 3131, 2181, 1611, 1528, 1501, 1411, 885 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.87-1.93 (2H, m), 2.12 (3H, s), 2.24 (3H, s), 3.53-3.67 (6H, m), 3.86-3.89 (2H, m), 6.65 (1H, d, J = 8.6 Hz), 7.34 (1H, dd, J = 2.0, 8.6 Hz), 7.91 (1H, d, J = 2.0 Hz), 8.82 (1H, br), 8.99 (1H, br);

MS (FAB) m/z: 316 $[M+H]^+$;

Anal. Calcd for $C_{16}H_{21}N_5S \cdot 0.3\ H_2O$: C, 59.90; H, 6.79; N, 21.83; S, 9.95. Found: C, 59.96; H, 6.62; N, 21.55; S, 10.19.

(106d) 3-amino-4-[4-(5-methylpyridin-2-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-[(4-(5-methylpyridin-2-yl)-1,4-diazepan-1-yl)but-2-enethioamide (1.26 g, 4.0 mmol) which was produced in Example 106 (106c) and N,N-dimethylformamide dimethylacetal (0.52 g, 4.4 mmol) were dissolved in N,N-dimethylformamide (6 mL) and the mixture was stirred at room temperature for one hour, and further stirred at 100°C for two hours. The reaction solution was cooled to room temperature and 8N aqueous solution of sodium hydroxide (1 mL) and 2-

chloroacetamide (0.49 g, 5.2 mmol) were added. Water (6 mL) was added after the mixture was stirred at room temperature for two hours. The deposited solid was separated by filtration, and 0.87 g of a crude product was obtained when washed with water and ethanol. The crude product was suspended in 80% aqueous ethanol (10 mL), and heated and the mixture was stirred and after it was cooled, the solid was separated by filtration and purified and 0.66 g of the title compound was obtained (yield 43%).

Mp 205-208°C;

IR (KBr) $\nu_{max}$ 3440, 3316, 3155, 1649, 1609, 1579, 1499, 1371, 939 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.08-2.15 (2H, m), 2.13 (3H, s), 3.15-3.28 (4H, m), 3.64-3.67 (2H, m), 3.92-3.98 (2H, m), 6.60 (1H, d, J = 8.6 Hz), 6.98 (2H, br), 7.04 (1H, d, J = 5.1 Hz), 7.07 (2H, br), 7.34 (1H, dd, J = 2.3, 8.6 Hz), 7.90 (1H, d, J = 2.0 Hz), 8.36 (1H, d, J = 5.1 Hz);

MS (EI) m/z: 382 [$M^+$];

Anal. Calcd for $C_{19}H_{22}N_6SO$: C, 59.66; H, 5.80; N, 21.97; S, 8.38. Found: C, 59.46; H, 5.93; N, 21.78; S, 8.41.

(Example 107)

3-amino-4-methoxythieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-1)

(107a) 2-chloro-4-methoxynicotinonitrile

A phosphorus oxychloride (10 mL) solution of 4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (1.50 g, 10 mmol) which was synthesized by a method of Ogawa et al. (Heterocycles, 36,145-148,1993) was heated under reflux for two hours. The reaction liquid was concentrated and a sodium hydrogen carbonate aqueous solution (10 mL) added to the obtained residual substance and the mixture was extracted with ethyl acetate (3x10 mL), and the solvent was evaporated under

reduced pressure after the extract was dried over sodium sulfate. The obtained residue was powderized with ether and the title compound was obtained (1.31 g, yield 78%).

Pale yellow powder

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 4.05 (3H, s), 7.40 (1H, d, J = 4.3 Hz), 8.55 (1H, d, J = 4.3 Hz).

(107b) 3-amino-4-methoxythieno[2,3-b]pyridine-2-carboxamide

2-mercaptoacetamide (109 mg, 1.2 mmol) and 8M aqueous solution of sodium hydroxide (0.4 mL) were added to N,N-dimethylformamide (2 mL) solution of 2-chloro-4-methoxynicotinonitrile (169 mg, 1.0 mmol) which was produced in Example 107 (107a), and the mixture was stirred at room temperature for one hour. Water (5 mL) was added to the reaction liquid and the resulted solid was separated by filtration and the title compound was obtained (92 mg, yield 41%).

Yellow powder

Mp 238-241°C;

IR (KBr) $\nu_{max}$ 3482, 3325, 3149, 1667, 1613, 1583, 1504, 1375, 1289, 1044 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 4.01 (3H, s), 6.95 (2H, brs), 6.98 (1H, d, J = 5.9 Hz), 7.05 (2H, brs), 8.46 (1H, d, J = 5.9 Hz);

HRMS m/z calcd for $C_9H_9N_3O_2S$ 223.0415, found 223.0416;

MS (EI) m/z: 223 [$M^+$], 205, 178, 150, 137, 122, 104, 77, 66, 45;

Anal. Calcd for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82; S, 14.36. Found: C, 48.11; H, 4.32; N, 18.76, S, 14.18.

(Example 108) 3-amino-4-ethoxythieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-2)

(108a) 2-chloro-4-ethoxynicotinonitrile

4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile, which was synthesized by a method of Ogawa et al. (Heterocycles, 36,145-148,1993) using triethyl orthoacetate in place of trimethyl orthoacetate, was used and the reaction was performed in a similar method as described in Example 107 (107a) and the title compound was synthesized.

Pale yellow powder

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.39 (3H, t, J = 6.8 Hz), 4.36 (2H, q, J = 6.8 Hz), 7.39 (1H, d, J = 6.4 Hz), 8.52 (1H, d, J = 6.4 Hz).

(108b) 3-amino-4-ethoxythieno[2,3-b]pyridine-2-carboxamide

2-chloro-4-ethoxynicotinonitrile was used in place of 2-chloro-4-methoxynicotinonitrile and the reaction was performed in a similar method as described in Example 107 (107b) and the title compound was synthesized.

Pale yellow powder

Mp 241-243°C;

IR (KBr) $\nu_{max}$ 3446, 3331, 1645, 1584, 1506, 1375, 1294, 1046 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 1.44 (3H, t, J = 7.1 Hz), 4.30 (2H, q, J = 7.1 Hz), 6.84 (2H, brs), 6.95 (1H, d, J = 5.9 Hz), 7.03 (2H, brs), 8.41 (1H, d, J = 5.9 Hz);

HRMS m/z calcd for $C_{10}H_{11}O_2N_3S$ 237.0572, found 237.0574;

MS (EI) m/z: 237 [$M^+$], 219, 205, 192, 176, 164, 148, 137, 120, 104;

Anal. Calcd for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71; S, 13.51. Found: C, 50.62; H, 4.69; N, 17.97, S, 13.52.

(Example 109) {[3-amino-2-(aminocarbonyl)thieno[2,3b]pyridin-4-yl]oxy}acetic acid (Exemplified Compound No. 1-5)

(109a) 2-chloro-4-oxo-1,4-dihydropyridine-3-carbonitrile

Concentrated hydrochloric acid (5 mL) was added to acetic acid (5 mL) solution of 2-chloro-4-methoxynicotinonitrile (0.98 g, 5.81 mmol) which was

produced in Example 107 (107a), and heated under reflux for two hours. Water (10 mL) was added to the reaction liquid and extracted with ethyl acetate (10 mL), and the solvent was evaporated under reduced pressure after the extract was dried over sodium sulfate. The obtained residue was powderized with ether and the title compound was obtained (0.35 g, yield 39%).

White powder

Mp 214-217°C;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 6.96 (1H, d, J = 5.9 Hz), 8.25 (1H, d, J = 5.9 Hz).

(109b) {[3-amino-2-(aminocarbonyl)thieno[2,3-b]pyridin-4-yl]oxy}acetic acid

Potassium carbonate (152 mg, 1.1 mmol) and bromoacetate tert-butyl ester (162 μL, 1.1 mmol) were added to N, N-dimethylacetamide (5 mL) solution of 2-chloro-4-oxo-1,4-dihydropyridine-3-carbonitrile (155 mg, 1.0 mmol) which was produced in Example 109 (109a) and the mixture was stirred at room temperature for five hours. Ethyl acetate (20 mL) and water (20 mL) were added to the reaction liquid and partitioned. The organic layer was washed with water (5x20 mL), a saline solution (20 mL) and the solvent was evaporated under reduced pressure after drying over sodium sulfate. The obtained residue was dissolved in N,N-dimethylformamide (2 mL) and was blended with 2-mercaptoacetamide (118 mg, 1.3 mmol) and 8N aqueous solution of sodium hydroxide (0.4 mL) and the mixture was stirred at room temperature for one hour. After 1N hydrochloric acid (4 mL) was added to the reaction liquid, it was concentrated under reduced pressure. The obtained residue was purified by reverse-phase chromatography (100% water) and the title compound was obtained (78 mg, yield 29%).

Yellow powder

Mp 248-249°C (decomposition);

IR (KBr) $\nu_{max}$ 3462, 3340, 3169, 1647, 1591, 1507, 1376, 1084 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 4.97 (2H, s), 6.93 (1H, d, J = 5.9 Hz), 7.04 (2H, brs), 7.07 (2H, brs), 8.44 (1H, d, J = 5.9 Hz);

HRMS m/z calcd for $C_{10}H_9O_4N_3S$ 267.0314, found 267.0325;

MS (FAB) m/z: 267 [$M^+$], 251, 205, 187, 69, 55;

Anal. Calcd for $C_{10}H_9N_3O_4S \cdot 1.96H_2O$: C, 39.70; H, 4.30; N, 13.89; S, 10.60. Found: C, 39.39; H, 3.99; N, 13.89; S, 10.46.

(Example 110) 3-amino-4-(benzyloxy)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-4)

Benzyl bromide was used in place of bromoacetic acid tert-butyl ester and the reaction was performed in a similar method as described in Example 109 (109b) and the title compound was synthesized.

White powder

Mp 216-221°C;

IR (KBr) $\nu_{max}$ 3490, 3324, 3151, 1651, 1580, 1502, 1370, 1290, 1039, 741 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 5.44 (2H, s), 6.89 (2H, brs), 7.04 (1H, d, J = 5.5 Hz), 7.07 (2H, brs), 7.36-7.55 (5H, m), 8.42 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{15}H_{13}O_2N_3S$ 299.0728, found 299.0730;

MS (FAB) m/z: 299 [$M^+$], 283, 273, 257, 200, 193, 165, 91, 65;

Anal. Calcd for $C_{15}H_{13}N_3O_2S \cdot 0.12H_2O$: C, 59.75; H, 4.43; N, 13.94; S, 10.63. Found: C, 60.09; H, 4.36; N, 13.63; S, 10.26.

(Example 111) 3-amino-4-isopropoxythieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-3)

(111a) 2,4-dichloronicotinonitrile

A phosphorus oxychloride (0.7 mL) solution of 2-chloro-4-oxo-1,4-dihydropyridine-3-carbonitrile (238 mg, 1.54 mmol) which was produced in

Example 109 (109a) was heated for two hours under reflux. The reaction liquid was concentrated and a sodium hydrogen carbonate aqueous solution (10 mL) was added to the obtained residual substance and extracted with ethyl acetate (10 mL) twice, and the solvent was evaporated under reduced pressure after drying over sodium sulfate. The obtained residue was powderized in hexane and the title compound was obtained (167 mg, yield 63%).

White powder

Mp 107-109°C;

IR (KBr) $\nu_{max}$ 3072, 2235, 1559, 1538, 1444, 1406, 1368, 1220, 820 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 7.91 (1H, d, J = 5.5 Hz), 8.65 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_6H_2N_2Cl_2$ 171.9595, found 171.9598;

MS (EI) m/z: 172 [$M^+$], 137, 110, 101, 75, 62, 51.

(111b) 2-chloro-4-isopropoxynicotinonitrile

sodium hydride (48 mg, 1.1 mmol) and N,N-dimethylacetamide (1 mL) solution of 2,4-dichloronicotinonitrile (173 mg, 1.00 mmol) which was produced in Example 111 (111a) were added to THF (1 mL) solution of 2-propanol (84 μL, 1.1 mmol) at 0°C and the mixture was stirred at room temperature for one hour. Water (3 mL) was added to the reaction liquid and generated powder was separated by filtration and the title compound was obtained (125 mg, yield 63%).

White powder

IR (KBr) $\nu_{max}$ 3096, 2985, 2235, 1580, 1550, 1469, 1390, 1316, 1262, 1102, 985, 840 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.36 (6H, d, J = 5.9 Hz), 4.99 (1H, quint, J = 5.9 Hz), 7.43 (1H, d, J = 6.4 Hz), 8.49 (1H, d, J = 6.4 Hz);

HRMS m/z calcd for $C_9H_9ON_2Cl$ 196.0404, found 196.0401;

MS (EI) m/z: 196 [$M^+$], 181, 154, 145, 126, 119, 111, 93, 71, 57, 44.

(111c) 3-amino-4-isopropoxythieno[2,3-b]pyridine-2-carboxamide

2-chloro-4-isopropoxynicotinonitrile which was produced in Example 111 (111b) was used in place of 2-chloro-4-methoxynicotinonitrile and the reaction was performed in a similar method as described in Example 107 (107b) and the title compound was obtained.

White powder

Mp 238-240°C (decomposition);

IR (KBr) $\nu_{max}$ 3485, 3322, 3137, 1672, 1616, 1582, 1506, 1378, 1287, 1107, 995 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.40 (6H, d, J = 6.3 Hz), 4.94 (1H, quint, J = 6.3 Hz), 6.83 (2H, brs), 6.98 (1H, d, J = 5.9 Hz), 7.02 (2H, brs), 8.39 (1H, d, J = 5.9 Hz);

HRMS m/z calcd for $C_{10}H_{13}O_2N_3S$ 251.0728, found 251.0742;

MS (EI) m/z: 251 [$M^+$], 209, 192, 180, 164, 137, 120, 103, 92, 66, 52, 42.

(Example 112) 3-amino-4-(cycloheptyloxy)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-8)

(112a) 2-chloro-4-(cycloheptyloxy)nicotinonitrile

Cycloheptyl alcohol was used in place of 2-propanol and the reaction was performed in a similar method as described in Example 111 (111b) and the title compound was synthesized.

Colourless liquid

IR (film) $\nu_{max}$ 2933, 2233, 1575, 1464, 1307, 998, 821 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.47-2.05 (12H, m), 4.64-4.69 (1H, m), 6.79 (1H, d, J = 6.3 Hz), 8.34 (1H, d, J = 6.3 Hz);

HRMS m/z calcd for $C_{13}H_{15}ON_2{}^{35}Cl$ 250.0873, found 250.0880;

MS (EI) m/z: 250 [$M^+$], 215, 172, 155, 137, 119, 97, 81, 55, 42;

Anal. Calcd for $C_{13}H_{15}ClN_2O \cdot 0.36H_2O$: C, 60.71; H, 6.16; N, 10.89. Found: C, 61.03; H, 6.51; N, 10.93.

(112b) 3-amino-4-(cycloheptyloxy)thieno[2,3-b]pyridine-2-carboxamide

2-chloro-4-(cycloheptyloxy)nicotinonitrile which was produced in Example 112 (112a) was used in place of 2-chloro-4-methoxynicotinonitrile and the reaction was performed in a similar method as described in Example 107 (107b) and the title compound was synthesized.

White powder

Mp 179-180°C;

IR (KBr) $\nu_{max}$ 3491, 3329, 3163, 2927, 1654, 1582, 1504, 1371, 1288, 1012 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.46-1.70 (8H, m), 1.81-1.90 (2H, m), 2.01-2.08 (2H, m), 4.83-4.89 (1H, m), 6.81 (2H, brs), 6.94 (1H, d, J = 5.5 Hz), 7.03 (2H, brs), 8.38 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{15}H_{19}O_2N_3S$ 305.1198, found 305.1197;

MS (EI) m/z: 305 [$M^+$], 209, 192, 164, 120, 97, 55, 41;

Anal. Calcd for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76; S, 10.50. Found: C, 58.81; H, 6.33; N, 13.60; S, 10.30.

(Example 113) 3-amino-4-(cyclohexyloxy)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-7)

(113a) 2-chloro-4-(cyclohexyloxy)nicotinonitrile

Cyclohexyl alcohol was used in place of 2-propanol and the reaction was performed in a similar method as described in Example 111 (111b) and the title compound was synthesized.

Colourless liquid

IR (film) $\nu_{max}$ 2941, 2862, 2233, 1578, 1465, 1305, 1016, 987, 824 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.42-1.96 (10H, m), 4.50-4.56 (1H, m), 6.84 (1H, d, J = 6.4 Hz), 8.35 (1H, d, J = 6.4 Hz);

HRMS m/z calcd for $C_{12}H_{13}ON_2Cl$ 236.0717, found 236.0721;

MS (EI) m/z: 236 [$M^+$], 207, 195, 181, 155, 119, 83, 67, 55, 42;

Anal. Calcd for $C_{12}H_{13}ClN_2O \cdot 0.12H_2O$: C, 60.34; H, 5.59; N, 11.73; Cl, 14.84. Found: C, 60.06; H, 5.85; N, 11.50; Cl, 15.24.

(113b) 3-amino-4-(cyclohexyloxy)thieno[2,3-b]pyridine-2-carboxamide

2-chloro-4-(cyclohexyloxy)nicotinonitrile which was produced in Example 113 (113a) was used in place of 2-chloro-4-methoxynicotinonitrile and the reaction was performed in a similar method as described in Example 107 (107b) and the title compound was synthesized.

White powder

Mp 206-208°C;

IR (KBr) $\nu_{max}$ 3492, 3330, 3159, 2935, 1654, 1580, 1504, 1368, 1286, 1041, 1020, 992 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.28-1.77 (8H, m), 1.94-2.03 (2H, m), 4.70-4.76 (1H, m), 6.81 (2H, brs), 7.02 (1H, d, J = 5.9 Hz), 7.04 (2H, brs), 8.38 (1H, d, J = 5.9 Hz);

HRMS m/z calcd for $C_{14}H_{17}O_2N_3S$ 291.1041, found 291.1040;

MS (EI) m/z: 291 [$M^+$], 209, 192, 164, 137, 120, 55, 41;

Anal. Calcd for $C_{14}H_{17}N_3O_2S \cdot 0.36H_2O$: C, 56.45; H, 6.00; N, 14.11; S, 10.76. Found: C, 56.75; H, 5.74; N, 14.07; S, 10.46.

(Example 114) 3-amino-4-(ethylthio)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-10)

(114a) 2-chloro-4-(ethylthio)nicotinonitrile

N,N -dimethylacetamide (1 mL) solution of sodium thioethoxide (93 mg, 1.1 mmol) was added to N,N -dimethylacetamide (1 mL) solution of 2,4-dichloronicotinonitrile (173 mg, 1.00 mmol) which was produced in Example 111 (111a) at 0°C and the mixture was stirred at room temperature for one hour. Water

(3 mL) was added to the reaction liquid, and generated powder was separated by filtration and further purified by silica gel column chromatography (hexane/ethyl acetate =3:1) and the title compound was obtained (44 mg, yield 22%).

Pale yellow powder

Mp 97-98°C;

IR (KBr) $\nu_{max}$ 2226, 1556, 1518, 1431, 1379, 1199, 819 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.46 (3H, t, J = 7.3 Hz), 3.12 (2H, q, J = 7.3 Hz), 7.11 (1H, d, J = 5.9 Hz), 8.33 (1H, d, J = 5.9 Hz);

HRMS m/z calcd for $C_8H_7N_2{}^{35}ClS$ 198.0018, found 198.0011;

MS (EI) m/z: 198 [$M^+$], 183, 170, 165, 147, 134, 126, 108, 98, 76, 69, 64, 46.

(114b) 3-amino-4-(ethylthio)thieno[2,3-b]pyridine-2-carboxamide

2-chloro-4-(ethylthio)nicotinonitrile which was produced in Example 114 (114a) was used in place of 2-chloro-4-methoxynicotinonitrile and the reaction was performed in a similar method as described in Example 107 (107b) and the title compound was obtained.

Pale yellow powder

Mp 230-235°C;

IR (KBr) $\nu_{max}$ 3460, 3297, 2141, 1666, 1589, 1494, 1365, 625 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.35 (3H, t, J = 7.4 Hz), 3.23 (2H, q, J = 7.4 Hz), 6.94 (2H, brs), 7.20 (2H, brs), 7.29 (1H, d, J = 5.5 Hz), 8.39 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{10}H_{11}ON_3S_2$ 253.0344, found 253.0333;

MS (EI) m/z: 253 [$M^+$], 236, 221, 208, 203, 193, 176, 148, 135, 104, 76, 45.

(Example 115) 3-amino-4-(cyclohexylthio)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-13)

Mercaptocyclohexane (116 mg, 1.00 mmol) and 8N aqueous solution of sodium hydroxide (0.19 mL) were added under ice-cooling to N,N-

dimethylacetamide (1 mL) solution of 2,4-dichloronicotinonitrile (173 mg, 1.00 mmol) which was produced in Example 111 (111a) and the mixture was stirred for one hour. The reaction mixture was partitioned with water and methylene chloride, and the organic layer was concentrated under reduced pressure after drying over sodium sulfate. The residue was purified by silica gel column chromatography (hexane/ethyl acetate =4:1) and a mixture (187 mg) of 2-chloro-4-(ethylthio)nicotinonitrile and 2,4-di(cyclohexylthio)nicotinonitrile was obtained. The obtained mixture (181 mg) and 2-mercaptoacetamide (66 mg) were dissolved in N,N-dimethylformamide (1.4 mL) and blended with 8N aqueous solution of sodium hydroxide (0.31 mL) and the mixture was stirred at room temperature for one hour. The solid which was deposited by adding water to the reaction mixture was separated by filtration and furthermore washed with ether and ethanol and the title compound was obtained 23 mg (yield 7%).

Yellow powder

Mp 195-197°C;

IR (KBr) $\nu_{max}$ 3450, 3310, 3154, 2929, 1662, 1585, 1495, 1363, 829, 620 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.39-2.04 (10H, m), 3.60-3.71 (1H, m), 7.06 (2H, brs), 7.19 (2H, brs), 7.38 (1H, d, J = 5.5 Hz), 8.41 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{14}H_{17}ON_3S_2$ 307.0813, found 307.0819;

MS (EI) m/z: 307 [$M^+$], 289, 262, 225, 208, 180, 136, 104, 83, 55, 41.

(Example 116) 3-amino-4-(4-{4-[(dimethylamino)carbonyl)phenyl}piperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-30)

(116a) tert-butyl 4-{4-[(dimethylamino)carbonyl]phenyl}piperazine-1-carboxylate

After 1,1'-carbonyldiimidazole (0.58 g, 3.6 mmol) was added to tetrahydrofuran (10 mL) solution of 4-[4-(tert-butoxycarbonyl)piperazin-1-yl]benzoic acid (1.00 g, 3.3 mmol) and the mixture was stirred at room temperature

for 30 minutes, 50% dimethylamine aqueous solution (0.45 mL) was added. The reaction liquid was stirred at room temperature for four hours and a saturated saline solution (100 mL) and ethyl acetate (100 mL) were added and partitioned. The organic layer was washed with a saturated sodium carbonate aqueous solution (30 mL) and the solvent was evaporated under reduced pressure after drying over sodium sulfate. The residue was purified by silica gel column chromatography (100% ethyl acetate) and 1.00 g of the title compound was obtained (yield 92%).

Mp 126-128°C;

IR (KBr) $\nu_{max}$ 1689, 1628, 1241, 1165, 835, 769 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 1.49 (9H, s), 3.06 (6H, brs), 3.20 (4H, t, J = 5.1 Hz), 3.58 (4H, t, J = 5.1 Hz), 6.89 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6);

MS (FAB) m/z: 333 [$M^+$];

Anal. Calcd for $C_{18}H_{27}N_3O_3$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.82; H, 8.41; N, 12.59.

(116b) N,N-dimethyl-4-piperazin-1-ylbenzamide

tert-butyl 4-{4-[(dimethylamino)carbonyl]phenyl}piperazine-1-carboxylate (1.00 g, 3.0 mmol) which was produced in Example 116 (116a) was dissolved in methanol (5 mL) and 4N hydrochloric acid-1,4-dioxane solution (5 mL) was added. After the reaction liquid was stirred at room temperature for two hours, it was concentrated under reduced pressure. 1N aqueous solution of sodium hydroxide (10 mL) was added to the obtained residue and the aqueous layer was extracted with methylene chloride (3x30 mL). After the extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure and the title compound was obtained 0.70 g (yield 100%).

Mp 108-112°C;

IR (KBr) $\nu_{max}$ 3312, 1611, 1388, 1243, 830, 766 $cm^{-1}$;

$^1$H NMR ($CDCl_3$, 400MHz) δ 1.75 (1H, br), 3.01-3.04 (4H, m), 3.05 (6H, s), 3.16-3.21 (4H, m), 6.87 (2H, d, J = 8.6 Hz), 7.35 (2H, d, J = 8.6);

MS (EI) m/z: 233 [$M^+$], 191;

Anal. Calcd for $C_{14}H_{21}N_3O \cdot 0.1\ H_2O$: C, 66.41; H, 8.23; N, 17.87. Found: C, 66.39; H, 8.30; N, 17.74.

(116c) 4-(4-[(1Z)-3-amino-2-cyano-1-methyl-3-thioxoprop-1-enyl]piperazin-1-yl)-N,N-dimethylbenzamide

N,N-dimethyl-4-piperazin-1-ylbenzamide which was produced in Example 116 (116b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 65%.

Mp 193-196°C;

IR (KBr) $\nu_{max}$ 3280, 3127, 2187, 1606, 1531, 992, 767 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 2.82 (3H, s), 2.95 (6H, s), 3.38-3.41 (4H, m), 3.54-3.57 (4H, m), 6.93 (2H, d, J = 7.8 Hz), 7.32 (2H, d, J = 7.8), 8.40 (1H, br), 9.12 (1H, br);

MS (FAB) m/z: 358 $[M+H]^+$;

Anal. Calcd for $C_{18}H_{23}N_5SO \cdot 0.2\ H_2O$: C, 59.88; H, 6.53; N, 19.40; S, 8.88. Found: C, 60.08; H, 6.47; N, 19.15; S, 8.72.

(116d) 4-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-piperazin-1-yl]-N,N-dimethylbenzamide

4-(4-[(1Z)-3-amino-2-cyano-1-methyl-3-thioxoprop-1-enyl]piperazin-1-yl)-N,N-dimethylbenzamide which was produced in Example 116 (116c) (650 mg, 1.82 mmol) and N,N-dimethylformamide dimethylacetal (238 mg, 265 μL, 2.00 mmol) were dissolved in N,N-dimethylformamide (10 mL) and the mixture was stirred at room temperature for one hour and at 60°C for a further two hours. Water (20 mL) was added to the reaction liquid and it was allowed to stand at room temperature for

two hours. The deposited solid was separated by filtration and, furthermore, washed with water and ethanol and the title compound was obtained 272 mg (yield 41%).

Mp 246-249°C;

IR (KBr) $\nu_{max}$ 2208, 1606, 1495, 1239, 985, 765 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.95 (6H, s), 3.40-3.43 (4H, m), 3.80-3.83 (4H, m), 6.53 (1H, d, J = 7.4 Hz), 6.92 (2H, d, J = 8.6 Hz), 7.30 (2H, d, J = 8.6 Hz), 7.50 (1H, d, J = 7.4 Hz), 12.70 (1H, br);

MS (FAB) m/z: 368 $[M+H]^+$;

Anal. Calcd for $C_{19}H_{21}N_5OS \cdot 1.2\ H_2O$: C, 58.65; H, 6.06; N, 18.00; S, 8.24. Found: C, 58.80; H, 6.06; N, 18.08; S, 8.18.

(116e) 3-amino-4-(4-{4-[(dimethylamino)carbonyl)phenyl}piperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed in a similar method as described in Example 5 (5c) using 4-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-piperazin-1-yl]-N,N-dimethylbenzamide which was produced in Example 116 (116d) and the title compound was obtained. Yield 82%.

Mp >270°C;

IR (KBr) $\nu_{max}$ 3447, 3327, 3180, 1652, 1625, 1606, 1577, 1238, 837, 767 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.96 (6H, s), 2.80-3.90 (8H, m), 6.97 (2H, br), 7.04 (2H, d, J = 8.2 Hz), 7.10 (1H, d, J = 5.1 Hz), 7.16 (2H, br), 7.34 (2H, d, J = 8.2 Hz), 8.48 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 425 $[M+H]^+$;

Anal. Calcd for $C_{21}H_{24}N_6O_2S \cdot 0.4\ H_2O$: C, 58.42; H, 5.79; N, 19.47; S, 7.43. Found: C, 58.56; H, 5.73; N, 19.48; S, 7.35.

(Example 117) 3-amino-4-(4-{4-[2-(dimethylamino)-2-oxoethyl)phenyl}piperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-429)

(117a) tert-butyl 4-{4-[2-(dimethylamino)-2-oxoethyl]phenyl}piperazine-1-carboxylate

Under a nitrogen atmosphere, 2-(4-bromophenyl) -N,N-dimethyl acetamide (J. Med. Chem. 33, (1990), 2899-2905.) (1.23 g, 5.1 mmol), tert-butyl 1-piperazinecarboxylate (1.13 g, 6.1), sodium tert-butoxide (0.69 g, 7.1 mmol), tris(dibenzylideneacetone) dipalladium (= Pd2(dba)3) (23 mg, 0.03 mmol) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino) biphenyl (39 mg, 0.10 mmol) were mixed in a mixed solvent of 1,4-dioxane (10 mL) and tert-butanol (5 mL) and the mixture was stirred under reflux for two hours.

Water (100 mL) and ethyl acetate (100 mL) were added to the reaction liquid mixture and insolubles were removed with Celite. The filtrate was partitioned and the aqueous layer was extracted with ethyl acetate (50 mL). After the combined organic layer was dried over sodium sulfate, the residue obtained by evaporating the solvent under reduced pressure was purified by silica gel column chromatography (100% ethyl acetate) and 1.59 g of the title compound was obtained (yield 91%).

Mp 110-112°C;

IR (KBr) $\nu_{max}$ 1689, 1639, 1431, 1169, 1129, 914 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 1.48 (9H, s), 2.96 (3H, s), 2.99 (3H, s), 3.09-3.11 (4H, m), 3.56-3.58 (4H, m), 3.64 (2H, s), 6.88 (2H, d, J = 8.2 Hz), 7.16 (2H, d, J = 8.2);

MS (FAB) m/z: 347 [$M^+$];

Anal. Calcd for $C_{19}H_{29}N_3O_3$: C, 65.58; H, 8.41; N, 12.09. Found: C, 65.58; H, 8.29; N, 11.89.

(117b) N,N-dimethyl-2-(4-piperazin-1-ylphenyl)acetamide

4N hydrochloric acid-1,4-dioxane solution (15 mL) was added to a methanol (15 mL) solution of tert-butyl 4-{4-[2-(dimethylamino)-2-

oxoethyl]phenyl}piperazine-1-carboxylate (1.89 g, 5.4 mmol) which was produced in Example 117 (117a) and the mixture was stirred at room temperature for two hours. 1N aqueous solution of sodium hydroxide (20 mL) was added to the residue which was obtained by concentrating the reaction mixture under reduced pressure and extracted with methylene chloride (3x50 mL). After the extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure and 1.30 g of the title compound was obtained (yield 97%).

Mp 90-92°C;

IR (KBr) $\nu_{max}$ 3269, 1637, 1517, 1241, 1128, 896 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.85 (1H, br), 2.94 (3H, s), 2.98 (3H, s), 3.01-3.03 (4H, m), 3.10-3.13 (4H, m), 3.62 (2H, s), 6.86 (2H, d, J = 8.6 Hz), 7.13 (2H, d, J = 8.6);

MS (EI) m/z: 247 [$M^+$], 205, 175;

Anal. Calcd for $C_{14}H_{21}N_3O \cdot 0.1\ H_2O$: C, 67.49; H, 8.58; N, 16.87. Found: C, 67.64; H, 8.24; N, 16.51.

(117c) 2-(4-{4-[(1Z)-3-amino-2-cyano-1-methyl-3-thioxoprop-1-enyl)piperazin-1-yl}phenyl) -N,N-dimethyl acetamide

N,N-dimethyl-2-(4-piperazin-1-ylphenyl)acetamide which was produced in Example (117b) was used in place of isobutylamine and the reaction was performed in a similar method as described in Example 5 (5a) and the title compound was obtained. Yield 90%.

Mp 174-177°C;

IR (KBr) $\nu_{max}$ 3283, 3141, 2189, 1622, 1537, 1518, 1236, 991 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.31 (3H, s), 2.81 (3H, s), 2.97 (3H, s), 3.23-3.26 (4H, m), 3.51-3.53 (4H, m), 3.56 (2H, s), 6.88 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 8.40 (1H, br), 9.11 (1H, br);

MS (FAB) m/z: 372 $[M + H]^+$;

Anal. Calcd for $C_{19}H_{25}N_5OS \cdot 0.2\ H_2O$: C, 60.84; H, 6.83; N, 18.67; S, 8.55. Found: C, 61.10; H, 6.65; N, 18.55; S, 8.46.

(117d) 2-{4-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-piperazin-1-yl]phenyl}-N,N-dimethyl acetamide

The reaction was performed in a similar method as described in Example 116 (116d) using 2-(4-{4-[(1Z)-3-amino-2-cyano-1-methyl-3-thioxoprop-1-enyl)piperazin-1-yl}phenyl) -N,N-dimethyl acetamide which was produced in Example 117 (117c). After the reaction terminated, the reaction liquid was partitioned with water (100 mL) and ethyl acetate (100 mL). The solid deposited in the aqueous layer was separated by filtration and washed with water and ethanol and 0.274 g of the title compound was obtained (yield 19%).

Mp 248-253°C;

1H NMR (DMSO-d6, 400MHz) δ 2.81 (3H, s), 2.97 (3H, s), 3.26-3.28 (4H, m), 3.57 (2H, s), 3.79-3.81 (4H, m), 6.56 (1H, d, J = 6.7 Hz), 6.90 (2H, d, J = 8.2 Hz), 7.09 (2H, d, J = 8.2 Hz), 7.53 (1H, d, J = 6.7 Hz), 12.76 (1H, br).

(117e) 3-amino-4-(4-{4-[2-(dimethylamino)-2-oxoethyl)phenyl}piperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed in a similar method as described in Example 5 (5c) using 2-{4-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-piperazin-1-yl]phenyl}-N,N-dimethyl acetamide which was produced in Example 117 (117d) and the title compound was obtained. Yield 94%.

Mp >280°C;

IR (KBr) $\nu_{max}$ 3437, 3318, 1629, 1571, 1382, 1244, 978, 962 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 2.82 (3H, s), 2.98 (3H, s), 2.80-3.80 (8H, m), 3.58 (2H, s), 6.95-6.97 (4H, m), 7.09-7.11 (4H, m), 7.13 (1H, d, J = 5.1 Hz), 8.47 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 439 $[M + H]^+$;

Anal. Calcd for $C_{22}H_{26}N_6O_2S \cdot 0.4\ H_2O$: C, 59.28; H, 6.06; N, 18.85; S, 7.19. Found: C, 59.43; H, 6.02; N, 18.98; S, 7.05.

(Example 118) 3-amino-4-(4-{3-[2-(dimethylamino)-2-oxoethyl)phenyl}piperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-430)

(118a) tert-butyl 4-{3-[2-(dimethylamino)-2-oxoethyl]phenyl}piperazine-1-carboxylate

The reaction was performed in a similar method as described in Example 117 (117a) using 2-(3-bromophenyl)-N,N-dimethyl acetamide (Arch.Pharm. (Weinheim) 321,315-320 (1988)) and the title compound was obtained as a viscous oil. Yield 92%.

IR (neat) $\nu_{max}$ 1685, 1635, 1241, 1171, 1124, 998, 772 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 1.48 (9H, s), 2.96 (3H, s), 2.99 (3H, s), 3.12-3.14 (4H, m), 3.55-3.57 (4H, m), 3.68 (2H, s), 6.76 (1H, brd, J = 8.0 Hz), 6.81 (1H, dd, J = 2.0, 8.0 Hz), 6.86 (1H, brs), 7.21 (1H, t, J = 8.0 Hz);

MS (FAB) m/z: 347 [$M^+$];

Anal. Calcd for $C_{19}H_{29}N_3O_3 \cdot 0.2\ H_2O$: C, 65.01; H, 8.44; N, 11.97. Found: C, 65.14; H, 8.08; N, 11.89.

(118b) N,N-dimethyl-2-(3-piperazin-1-ylphenyl)acetamide

The reaction was performed in a similar method as described in Example 117 (117b) using tert-butyl 4-{3-[2-(dimethylamino)-2-oxoethyl]phenyl}piperazine-1-carboxylate which was produced in (118a) and an oily title compound was synthesized. Yield 99%.

IR (neat) $\nu_{max}$ 3456, 3316, 1640, 1244, 995, 772 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 2.08 (1H, br), 2.96 (3H, s), 2.99 (3H, s), 3.02-3.05 (4H, m), 3.15-3.17 (4H, m), 3.68 (2H, s), 6.74 (1H, brd, J = 7.4 Hz), 6.81 (1H, dd, J = 2.3, 8.2 Hz), 6.85 (1H, brs), 7.20 (1H, dd, J = 7.4, 8.2 Hz);

MS (EI) m/z: 247 [$M^+$], 205.

(118c) 2-{3-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-piperazin-1-yl]phenyl}-N,N-dimethyl acetamide

N,N-dimethyl-2-(3-piperazin-1-ylphenyl)acetamide (2.68 g, 10.8 mmol) which was produced in Example 118 (118b) and (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J. Org. Chem. (1962), 27,2433-2439) (1.54 g, 9.0 mmol) were mixed in ethanol (30 mL) and the mixture was stirred at room temperature for 15 hours. The residue which was obtained by evaporating the solvent under reduced pressure was dissolved in N,N-dimethylformamide (30 mL) and N,N-dimethylformamide dimethylacetal (1.29 g, 1.44 mL, 10.8 mmol) was added. The reaction mixture was stirred at room temperature for one hour and further at 80°C for two hours. After cooling to room temperature, the reaction mixture was partitioned with a saturated saline solution (100 mL) and ethyl acetate (100 mL) and the aqueous layer was extracted with methylene chloride (3x50 mL). After the extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (methylene chloride/methanol =20:1) and 0.329 g of the title compound was obtained (yield 10%).

Mp 250-254°C;

IR (KBr) $\nu_{max}$ 2206, 1602, 1496, 1238, 985, 772 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.81 (3H, s), 2.98 (3H, s), 3.27-3.29 (4H, m), 3.61 (2H, s), 3.78-3.81 (4H, m), 6.53 (1H, d, J = 7.4 Hz), 6.65 (1H, brd, J = 7.4 Hz), 6.78-6.80 (2H, m), 7.14 (1H, dd, J = 7.4, 9.0 Hz), 7.49-7.52 (1H, m), 12.72 (1H, br);

MS (FAB) m/z: 382 $[M + H]^+$;

Anal. Calcd for $C_{20}H_{23}N_5OS \cdot 0.4\ H_2O$: C, 61.80; H, 6.17; N, 18.02; S, 8.25. Found: C, 61.77; H, 6.07; N, 18.04; S, 8.18.

(118d) 3-amino-4-(4-{3-[2-(dimethylamino)-2-oxoethyl)phenyl}piperazin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed in a similar method as described in Example 5 (5c) using 2-{3-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-piperazin-1-yl]phenyl}-N,N-dimethyl acetamide which was produced in (118c) and the title compound was obtained. Yield 78%.

Mp 273-275°C;

IR (KBr) $\nu_{max}$ 3439, 3316, 1632, 1579, 1370, 1240, 976, 771 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.83 (3H, s), 3.00 (3H, s), 2.80-3.80 (8H, m), 3.64 (2H, s), 6.59 (1H, d, J = 7.4 Hz), 6.87-6.90 (2H, m), 6.97 (2H, brs), 7.10 (1H, d, J = 5.5 Hz), 7.15 (2H, brs), 7.18 (1H, dd, J = 7.4, 8.6 Hz), 8.48 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 439 $[M + H]^+$;

Anal. Calcd for $C_{22}H_{26}N_6O_2S \cdot 0.1\ H_2O$: C, 60.01; H, 6.00; N, 19.08; S, 7.28. Found: C, 59.97; H, 5.97; N, 19.09; S, 7.07.

(Example 119) 3-amino-4-{4-[4-(1-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1007)

Sodium borohydride (95 mg, 2.5 mmol) was added to a methanol (6 mL) suspension of 4-[4-(4-acetylphenyl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide (103 mg, 0.25 mmol) which was produced in Example 94, and heated under reflux for two days. Water (30 mL) was added to the reaction liquid and the deposited solid was separated by filtration and the title compound was obtained (95 mg, yield 92%).

Yellow powder

Mp 244-248°C;

IR (KBr) $\nu_{max}$ 3450, 3337, 1646, 1609, 1518, 1368, 1187, 823 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.29 (3H, d, J = 6.4 Hz), 2.12-2.14 (2H, m), 3.20 (2H, brs), 3.29 (2H, brs), 3.54 (2H, t, J = 6.3 Hz), 3.76 (2H, t, J = 5.0 Hz), 4.60 (1H, t, J = 4.9 Hz), 4.83 (1H, d, J = 4.4 Hz), 6.72 (2H, d, J = 8.2 Hz), 6.97 (2H, brs), 7.08 (1H, d, J = 5.4 Hz), 7.08 (2H, brs), 7.15 (2H, d, J = 8.8 Hz), 8.40 (1H, d, J = 5.4 Hz);
HRMS m/z calcd for $C_{21}H_{26}O_2N_5S$ 412.1807, found 412.1815;
MS (FAB) m/z: 411 [$M^+$], 394, 273, 242, 183, 166, 120, 65, 51, 39, 31;
Anal. Calcd for $C_{21}H_{25}N_5O_2S \cdot 0.34H_2O$: C, 60.39; H, 6.20; N, 16.77; S, 7.68. Found: C, 60.32; H, 6.06; N, 16.72; S, 7.61.

(Example 120) 3-amino-4-{4-[4-(N-hydroxyethaneimidoyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1037)

Hydroxylamine hydrochloride (97 mg, 1.4 mmol) and sodium acetate (115 mg, 1.4 mmol) were added to a methanol (3 mL) suspension of 4-[4-(4-acetylphenyl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide (56 mg, 0.14 mmol) which was produced in Example 94, and heated under reflux for two days. Water (10 mL) was added to the reaction liquid and the deposited solid was separated by filtration and the title compound was obtained (33 mg, yield 56%).
Pale yellow powder
Mp 238-241°C;
IR (KBr) $\nu_{max}$ 3431, 3317, 3169, 1643, 1601, 1521, 1370, 1200, 908, 826, 561, 482 $cm^{-1}$;
$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 2.09 (3H, s), 2.13-2.16 (2H, m), 3.19 (2H, brs), 3.29-3.32 (2H, m), 3.59 (2H, t, J = 6.4 Hz), 3.80 (2H, t, J = 4.9 Hz), 6.78 (2H, d, J = 8.8 Hz), 6.99 (2H, brs), 7.09 (1H, d, J = 5.4 Hz), 7.09 (2H, brs), 7.49 (2H, d, J = 8.8 Hz), 8.41 (1H, d, J = 5.4 Hz), 10.71 (1H, s);
HRMS m/z calcd for $C_{21}H_{25}O_2N_6S$ 425.1760, found 425.1761;
MS (FAB) m/z: 425 [$M^+$], 407, 273, 246, 228, 182, 65;

Anal. Calcd for $C_{21}H_{24}N_6O_2S \cdot 0.5H_2O$: C, 58.18; H, 5.81; N, 19.39; S, 7.40. Found: C, 58.39; H, 5.80; N, 19.26; S, 7.27.

(Example 121) 3-amino-4-[4-(4-propionylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-100)

(121a) tert-butyl 4-(4-propionylphenyl)-1,4-diazepane-1-carboxylate

4-fluoropropiophenone was used in place of 4-fluoro nitrobenzene and the reaction was performed in a similar method as described in Example 59 (59a) and the title compound was obtained (yield 45%).

Yellow oil

IR (film) $\nu_{max}$ 2975, 2936, 1693, 1669, 1599, 1523, 1416, 1365 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.20 (3H, t, J = 7.4 Hz), 1.35 (4.5H, s), 1.42 (4.5H, s), 1.92-2.02 (2H, m), 2.89 (2H, q, J = 7.4 Hz), 3.18-3.24 (1H, m), 3.29-3.34 (1H, m), 3.54-3.66 (6H, m), 6.66 (2H, d, J = 9.0 Hz), 7.85 (2H, d, J = 9.0 Hz);

MS (FAB) m/z: 332 $M^+\cdot$, 277, 259, 231.

(121b) 1-[4-(1,4-diazepan-1-yl)phenyl]propan-1-one

The reaction was performed in a similar method as described in Example 57 (57b) using tert-butyl 4-(4-propionylphenyl)-1,4-diazepane-1-carboxylate which was produced in Example 121 (121a) and the title compound was obtained (yield 95%).

Pale brown prism crystal

Mp 97-98°C;

IR (KBr) $\nu_{max}$ 3343, 2935, 2821, 1652, 1597, 1524, 1407 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.20 (3H, t, J = 7.4 Hz), 1.87-1.95 (2H, m), 2.80-2.85 (2H, m), 2.89 (2H, q, J = 7.4 Hz), 3.01-3.07 (2H, m), 3.58-3.67 (4H, m), 6.65 (2H, d, J = 9.0 Hz), 7.85 (2H, d, J = 9.0 Hz);

MS (EI) m/z: 232 $M^+\cdot$, 203, 190, 176.

(121c) 4-[4-(4-propionylphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

N,N-dimethylformamide (8.47 mL) solution of 1-[4-(1,4-diazepan-1-yl)phenyl]propan-1-one (984 mg, 4.24 mmol) produced in Example 121 (121b) was blended with (2Z) -2-cyano-3-ethoxybut-2-enethioamide (J.Org.Chem. (1962), 27,2433-2439) (721 mg, 4.24 mmol) and the mixture was stirred at room temperature for 15 minutes. Then N,N-dimethylformamide dimethylacetal (619 μL, 4.66 mmol) was added and after stirring for one hour, it was heated and the mixture was stirred at 80°C for 30 minutes. After the reaction liquid was allowed to be cooled to room temperature, it was blended with ethyl acetate (8.5 mL) and water (21 mL) and the mixture was stirred for 30 minutes. The deposited crystal was separated by filtration, washed sequentially with ethyl acetate and water and then dried and 508 mg of the title compound (yield 33%) was obtained.

Pale brown powder

Mp 157-158°C;

IR (KBr) $\nu_{max}$ 3443, 3353, 3277, 3176, 2926, 2182, 1617, 1525, 1346 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.04 (2H, t, J = 7.3 Hz), 1.90-1.99 (2H, m), 2.87 (2H, q, J = 7.3 Hz), 3.63 (2H, t, J = 5.9 Hz), 3.73-3.78 (2H, m), 3.83-3.88 (2H, m), 3.95-4.00 (2H, m), 6.44 (1H, d, J = 7.8 Hz), 6.84 (2H, d, J = 8.8 Hz), 7.37 (1H, d, J = 7.8 Hz), 7.78 (2H, d, J = 8.8 Hz), 12.53 (1H, br.s);

MS (FAB) m/z: 367 $[M+H]^+$, 273, 246, 228;

Anal. Calcd for $C_{20}H_{22}N_4OS \cdot 0.4H_2O$: C, 64.28; H, 6.15; N, 14.99; S, 8.58. Found: C, 64.15; H, 6.23; N, 15.26; S, 8.50.

(121d) 3-amino-4-[4-(4-propionylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed in a similar method as described in Example 5 (5c) using 4-[4-(4-propionylphenyl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 121 (121c) and the title compound was obtained. Yield 65%.

Pale yellow powder

Mp 231-233°C;

IR (KBr) $\nu_{max}$ 3440, 3326, 3186, 2934, 1648, 1597, 1368 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.06 (3H, t, J = 7.4 Hz), 2.11-2.21 (2H, m), 2.89 (2H, q, J = 7.4 Hz), 3.13-3.24 (2H, m), 3.25-3.34 (2H, m), 3.64 (2H, t, J = 5.1 Hz), 3.82-3.90 (2H, m), 6.82 (2H, d, J = 9.0 Hz), 6.97 (2H, br.s), 7.06 (1H, d, J = 5.1 Hz), 7.09 (2H, br.s), 7.79 (2H, d, J = 9.0 Hz), 8.38 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 424 $[M+H]^+$, 423, 407;

Anal. Calcd for $C_{22}H_{25}N_5O_2S \cdot 0.4H_2O$: C, 61.35; H, 6.04; N, 16.26; S, 7.44. Found: C, 61.43; H, 6.23; N, 16.10; S, 7.34.

(Example 122)

3-amino-4-(4-{4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1082)

(122a) 2-(4-bromobenzyl)-2-methyl-1,3-dioxolane

Ethylene glycol (1.67 mL, 30.0 mmol), p-toluenesulfonic acid monohydrate (380 mg, 2.0 mmol) were added to toluene (100 mL) solution of 1-(4-bromophenyl) acetone (4.26 g, 20.0 mmol) and the mixture was stirred at 120°C for nine hours. The solvent was evaporated under reduced pressure after an excess amount of triethylamine was added to the reaction liquid. The obtained residual substance was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) and the title compound was obtained (4.80 g, 93%).

Pale yellow liquid

IR (film) $\nu_{max}$ 2983, 2882, 1489, 1376, 1128, 1047, 832 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.30 (3H, s), 2.87 (2H, s), 3.67-3.73 (2H, m), 3.84-3.92 (2H, m), 7.13 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz);

MS (EI) m/z: 256 [$M^+$], 243, 241, 171, 169, 87, 43.

(122b) benzyl 4-{4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}-1,4-diazepane-1-carboxylate

Reaction with benzyl 1-homopiperazinecarboxylate was performed in a similar method as described in 117 (117a) using 2-(4-bromobenzyl)-2-methyl-1,3-dioxolane which was produced in Example 122 (122a) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2942, 1700, 1614, 1520, 1421, 1222, 1118, 1046, 927 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.29 (3H, s), 1.91-2.07 (2H, m), 2.81 (2H, s), 3.30 (1H, t, J = 5.9 Hz), 3.37 (1H, t, J = 5.9 Hz), 3.49-3.68 (6H, m), 3.76-3.83 (2H, m), 3.88-3.93 (2H, m), 5.09 (1H, s), 5.33 (1H, s), 6.62 (2H, d, J = 8.6 Hz), 7.11 (2H, d, J = 8.6 Hz), 7.26-7.39 (5H, m);

MS (FAB) m/z: 411 [$M+H^+$], 323, 275, 87.

(122c) 1-{4-[(2-methyl-1,3-dioxolan-2-yl) methyl]phenyl}-1,4-diazepane

Hydrogenolysis reaction was performed in the presence of a palladium-carbon catalyst in ethanol using benzyl 4-{4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}-1,4-diazepane-1-carboxylate which was produced in Example 122 (122b), and the title compound was obtained.

Pale yellow liquid

IR (film) $\nu_{max}$ 3319, 2935, 1614, 1520, 1375, 1191, 1045, 813 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.30 (3H, s), 1.82-1.93 (2H, m), 2.80 (2H, s), 2.82 (2H, t, J = 5.9 Hz), 3.02 (2H, t, J = 5.5 Hz), 3.53 (2H, t, J = 5.5 Hz), 3.56 (2H, t, J = 5.9 Hz), 3.76-3.82 (2H, m), 3.87-3.93 (2H, m), 6.63 (2H, d, J = 8.6 Hz), 7.10 (2H, d, J = 8.6 Hz);
MS (EI) m/z: 276 [$M^+$], 190, 189, 87.

(122d) 4-(4-{4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) using 1-{4-[(2-methyl-1,3-dioxolan-2-yl) methyl]phenyl}-1,4-diazepane which was produced in Example 122 (122c) and the title compound was obtained.
Brown powder
Mp 204-206°C;
IR (KBr) $\nu_{max}$ 2949, 2206, 1625, 1518, 1353, 1247, 1139, 1043, 930, 781 $cm^{-1}$;
$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.15 (3H, s), 1.90-1.97 (2H, m), 2.67 (2H, s), 3.51 (2H, t, J = 5.9 Hz), 3.57-3.64 (2H, m), 3.68-3.80 (6H, m), 3.94 (2H, t, J = 5.9 Hz), 6.41 (1H, d, J = 7.8 Hz), 6.67 (2H, d, J = 8.3 Hz), 7.01 (2H, d, J = 8.3 Hz), 7.34 (1H, d, J = 7.8 Hz), 12.50 (1H, brs);
MS (FAB) m/z: 411 [M+$H^+$], 367, 338, 273, 246;
Anal. Calcd for $C_{22}H_{26}N_4O_2S \cdot 0.25H_2O$: C, 63.67; H, 6.44; N, 13.50. Found: C, 63.90; H, 6.18; N, 13.45.

(122e) 3-amino-4-(4-{4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}-1,4- diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-(4-{4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}-1,4-diazepan-1-yl)-2-

thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 122 (122d) and the title compound was obtained.

Pale yellow powder

Mp 227-229°C;

IR (KBr) $\nu_{max}$ 3446, 3333, 3143, 2923, 1643, 1575, 1515, 1372, 1212, 1044, 825 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.16 (3H, s), 2.06-2.19 (2H, m), 2.70 (2H, s), 3.13-3.22 (2H, m), 3.23-3.32 (2H, m), 3.51 (2H, t, J = 5.9 Hz), 3.69-3.86 (6H, m), 6.66 (2H, d, J = 8.6 Hz), 6.98 (2H, brs), 7.02 (2H, d, J = 8.6 Hz), 7.05 (1H, d, J = 5.5 Hz), 7.07 (2H, brs), 8.37 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 468 [$M+H^+$], 273, 246, 165, 93, 63;

Anal. Calcd for $C_{24}H_{29}N_5O_3S \cdot 0.20H_2O$: C, 61.18; H, 6.29; N, 14.86. Found: C, 61.19; H, 6.25; N, 14.81.

(Example 123) 3-amino-4-{4-[4-(2-oxopropyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1019)

1N hydrochloric acid (2.0 mL) was added to a methanol (2.0 mL) solution of 3-amino-4-(4-{4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (200 mg, 428 μ mol) which was produced in Example 122 and the mixture was stirred at room temperature for two hours. The solvent was evaporated under reduced pressure after an excess amount of triethylamine was added to the reaction liquid. The obtained residual substance was blended with methylene chloride/2-propanol (4:1) (100 mL) and washed with water (50 mL) and the solvent was evaporated under reduced pressure after drying over sodium sulfate. The obtained powder was washed with ethanol and the title compound was obtained (160 mg, 88%).

Pale yellow powder

Mp 225-230°C;

IR (KBr) $\nu_{max}$ 3440, 3325, 3150, 2946, 1648, 1576, 1517, 1370, 1232, 939, 819 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.08 (3H, s), 2.09-2.18 (2H, m), 3.17-3.23 (2H, m), 3.25-3.33 (2H, m), 3.53 (2H, t, J = 5.4 Hz), 3.57 (2H, s), 3.75 (2H, t, J = 5.4 Hz), 6.73 (2H, d, J = 8.8 Hz), 7.00 (2H, brs), 7.01 (2H, d, J = 8.8 Hz), 7.07 (1H, d, J = 5.4 Hz), 7.09 (2H, brs), 8.40 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 424 [$M+H^+$], 407, 380, 273, 258, 220, 165, 63;

Anal. Calcd for $C_{22}H_{25}N_5O_2S \cdot 0.32H_2O$: C, 61.55; H, 6.02; N, 16.31. Found: C, 61.94; H, 6.12; N, 15.88.

(Example 124) 3-amino-4-{4-[4-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1003)

(124a) benzyl 4-[4-(2-hydroxyethyl)phenyl]-1,4-diazepane-1-carboxylate

The reaction was performed following a method described in Example 117 (117a) using benzyl 1-homopiperazinecarboxylate and 4-bromophenethyl alcohol and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 3444, 2939, 1696, 1519, 1423, 1230, 1040 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.91-2.05 (2H, m), 2.76 (2H, t, J = 6.8 Hz), 3.31 (1H, t, J = 5.9 Hz),3.38 (1H, t, J = 5.9 Hz), 3.49-3.68 (6H, m), 3.77-3.85 (2H, m), 5.09 (1H, s), 5.13 (1H, s), 6.62-6.68 (m, 2H), 7.05-7.10 (2H, m), 7.27-7.38 (5H, m);

MS (EI) m/z: 354 [$M^+$], 323, 263, 233, 202, 190, 176, 91.

(124b) 2-[4-(1,4-diazepan-1-yl)phenyl]ethanol

Hydrogenolysis reaction was performed in the presence of a palladium-carbon catalyst in ethanol using benzyl 4-[4-(2-hydroxyethyl)phenyl]-1,4-diazepane-1-

carboxylate which was produced in Example 124 (124a) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 3399, 2934, 1615, 1520, 1414, 1190, 1048, 808 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.83-1.94 (2H, m), 2.76 (2H, t, J = 6.6 Hz), 2.83 (2H, t, J = 5.9 Hz), 3.02 (2H, t, J = 5.5 Hz), 3.53 (2H, t, J = 5.5 Hz), 3.56 (2H, t, J = 5.9 Hz), 3.80 (2H, t, J = 6.6 Hz), 6.66 (2H, d, J = 9.0 Hz), 7.07 (2H, d, J = 9.0 Hz);

MS (EI) m/z: 220 [$M^+$], 56.

(124c) 4-{4-[4-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) using 2-[4-(1,4-diazepan-1-yl)phenyl]ethanol which was produced in Example 124 (124b) and the title compound was synthesized.

Brown powder

Mp 180-185°C;

IR (KBr) $\nu_{max}$ 2939, 2206, 1625, 1517, 1354, 1250, 1042, 928, 805 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.88-1.97 (2H, m), 2.57 (2H, t, J = 7.4 Hz), 3.44-3.55 (4H, m), 3.66-3.74 (4H, m), 3.90-3.97 (2H, m), 4.53 (1H, brs), 6.41 (1H, d, J = 7.4 Hz), 6.67 (2H, d, J = 8.6 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.34 (1H, d, J = 7.4 Hz), 12.50 (1H, brs);

MS (FAB) m/z: 355 [M+$H^+$], 273, 257, 242, 176, 165, 120, 63;

Anal. Calcd for $C_{19}H_{22}N_4OS \cdot 0.25H_2O$: C, 63.57; H, 6.32; N, 15.61. Found: C, 63.36; H, 6.00; N, 15.61.

(124d) 3-amino-4-{4-[4-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-{4-[4-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 124 (124c) and the title compound was synthesized.

White powder

Mp 257-262°C;

IR (KBr) $\nu_{max}$ 3445, 3324, 3151, 2939, 1655, 1576, 1516, 1370, 1232, 1045, 938, 807 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.07-2.16 (2H, m), 2.59 (2H, t, J = 7.4 Hz), 3.13-3.23 (2H, m), 3.24-3.30 (2H, m), 3.47-3.56 (4H, m), 3.67-3.77 (2H, m), 4.54 (1H, t, J = 5.1 Hz), 6.67 (2H, d, J = 8.6 Hz), 6.95 (2H, brs), 6.99 (2H, d, J = 8.6 Hz), 7.05 (1H, d, J = 5.5 Hz), 7.07 (2H, brs), 8.37 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 412 [$M+H^+$], 242, 165, 120, 63;

Anal. Calcd for $C_{21}H_{25}N_5O_2S \cdot 0.30H_2O$: C, 60.50; H, 6.19; N, 16.80. Found: C, 60.43; H, 6.08; N, 16.79.

(Example 125)

3-amino-4-{4-[4-(2-methoxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-876)

(125a) 1-bromo-4-(2-methoxyethyl)benzene

N,N-dimethylformamide (20 mL) solution of 4-bromophenethyl alcohol (2.01 g, 10.0 mmol) was cooled to 0°C and was blended with sodium hydride (55% oily, 436 mg, 10.0 mmol) and the mixture was stirred at 0°C for 10 minutes. The reaction mixture was blended with methyl iodide (0.75 mL, 12.0 mmol) and the mixture was stirred at room temperature for a further three hours. Water (50 mL) was added to the reaction liquid and extracted with ethyl acetate (50 mL) three times. The organic layers were combined and washed with water (50 mL) and a saturated

saline solution (50 mL), and the solvent was evaporated under reduced pressure after drying over sodium sulfate and the title compound was obtained (2.15 g, yield 100%).

Yellow liquid

IR (film) $\nu_{max}$ 2925, 1489, 1382, 1191, 1117, 1011, 804 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 2.83 (2H, t, J = 7.0 Hz), 3.34 (3H, s), 3.58 (2H, t, J = 7.0 Hz), 7.10 (2H, d, J = 8.2 Hz), 7.41 (2H, d, J = 8.2 Hz);

MS (EI) m/z: 214 [$M^+$], 171, 169, 135, 104, 90, 45.

(125b) benzyl 4-[4-(2-methoxyethyl)phenyl]-1,4-diazepane-1-carboxylate

Reaction with benzyl 1-homopiperazinecarboxylate was performed following a method described in Example 117 (117a) using 1-bromo-4-(2-methoxyethyl)benzene which was produced in Example 125 (125a) and the title compound was synthesized.

Yellow liquid

IR (film) $\nu_{max}$ 2932, 1699, 1615, 1520, 1421, 1228, 928 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.88-2.05 (2H, m), 2.78 (2H, t, J = 7.0 Hz), 3.25-3.41 (5H, m), 3.47-3.67 (8H, m), 5.08 (1H, s), 5.13 (1H, s), 6.59-6.67 (2H, m), 7.03-7.10 (2H, m), 7.27-7.38 (5H, m);

MS (EI) m/z: 368 [$M^+$], 324, 323, 277, 233, 216, 190, 178, 160, 146, 118, 107, 91, 70, 44.

(125c) 1-[4-(2-methoxyethyl)phenyl]-1,4-diazepane

Hydrogenolysis reaction was performed in the presence of a palladium-carbon catalyst in ethanol using benzyl 4-[4-(2-methoxyethyl)phenyl]-1,4-diazepane-1-carboxylate which was produced in Example 125 (125b) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 3327, 2930, 1615, 1520, 1393, 1191, 1113, 807 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.83-1.92 (2H, m), 2.77 (2H, t, J = 7.0 Hz), 2.82 (2H, t, J = 5.9 Hz), 3.01 (2H, t, J = 5.9 Hz), 3.35 (3H, s), 3.49-3.57 (6H, m), 6.62 (2H, d, J = 8.6 Hz), 7.04 (2H, d, J = 8.6 Hz);

MS (FAB) m/z: 234 [$M^+$], 204, 189, 178, 164, 146, 132, 118, 105, 91, 70.

(125d) 4-{4-[4-(2-methoxyethyl)phenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) using 1-[4-(2-methoxyethyl)phenyl]-1,4-diazepane which was produced in Example 125 (125c) and the title compound was synthesized.

Brown powder

Mp 182-185°C;

IR (KBr) $\nu_{max}$ 2930, 2204, 1625, 1518, 1353, 1241, 1109, 929, 805 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.89-1.98 (2H, m), 2.65 (2H, t, J = 7.3 Hz), 3.22 (3H, s), 3.44 (2H, t, J = 7.3 Hz), 3.50 (2H, t, J = 5.9 Hz), 3.68-3.75 (4H, m), 3.92-3.97 (2H, m), 6.42 (1H, d, J = 7.8 Hz), 6.70 (2H, d, J = 8.8 Hz), 7.01 (2H, d, J = 8.8 Hz), 7.36 (1H, d, J = 7.8 Hz), 12.50 (1H, brs);

MS (FAB) m/z: 369 [$M+H^+$], 336, 323, 273, 246, 165;

Anal. Calcd for $C_{20}H_{24}N_4OS \cdot 0.25H_2O$: C, 64.40; H, 6.62; N, 15.02. Found: C, 64.43; H, 6.52; N, 14.80.

(125e) 3-amino-4-{4-[4-(2-methoxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using

4-{4-[4-(2-methoxyethyl)phenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 125 (125d) and the title compound was synthesized.

Pale yellow powder

Mp 230-235°C;

IR (KBr) $\nu_{max}$ 3443, 3169, 2935, 1655, 1573, 1518, 1452, 1369, 1231, 1102, 938, 807 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.09-2.17 (2H, m), 2.68 (2H, t, J = 7.3 Hz), 3.15-3.23 (2H, m), 3.24 (3H, s), 3.26-3.31 (2H, m), 3.46 (2H, t, J = 7.3 Hz), 3.52 (2H, t, J = 5.9 Hz), 3.71-3.78 (2H, m), 6.69 (2H, d, J = 8.8 Hz), 6.98 (2H, brs), 7.03 (2H, d, J = 8.8 Hz), 7.07 (1H, d, J = 5.4 Hz), 7.08 (2H, brs), 8.40 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 426 [$M+H^+$], 409, 380, 273, 230;

Anal. Calcd for $C_{22}H_{27}N_5O_2S \cdot 0.25H_2O$: C, 61.44; H, 6.45; N, 16.28. Found: C, 61.26; H, 6.40; N, 16.09.

(Example 126)

3-amino-4-{4-[3-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1004)

(126a) 1-[2-(benzyloxy)ethyl]-3-bromobenzene

N,N-dimethylformamide (20 mL) solution of 3-bromophenethyl alcohol (2.04 g, 10.0 mmol) was cooled to 0°C and was blended with sodium hydride (55% oily, 436 mg, 10.0 mmol) and the mixture was stirred at 0°C for 15 minutes. Then the reaction mixture was blended with methyl iodide (1.40 mL, 12.0 mmol) and the mixture was stirred at room temperature for two hours. Water (50 mL) was added to the reaction liquid and extracted with ethyl acetate (50 mL) three times. The organic layers were combined and washed with water (50 mL) and a saturated saline solution (50 mL), the solvent was evaporated under reduced pressure after drying

over sodium sulfate, the obtained residue was purified by silica gel column chromatography (hexane/toluene = 3:1) and the title compound was obtained (2.60 g, 89%).

Colourless liquid

IR (film) $\nu_{max}$ 2858, 1568, 1475, 1361, 1203, 1103, 695 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 2.88 (2H, t, J = 7.0 Hz), 3.66 (2H, t, J = 7.0 Hz), 4.50 (2H, s), 7.11-7.15 (2H, m), 7.23-7.38 (7H, m);

MS (EI) m/z: 292, 290 [$M^+$], 262, 260, 184, 169, 91.

(126b) benzyl 4-{3-[2-(benzyloxy)ethyl]phenyl}-1,4-diazepane-1-carboxylate

Reaction with benzyl 1-homopiperazinecarboxylate was performed following a method described in Example 117 (117a) using 1-[2-(benzyloxy)ethyl]-3-bromobenzene which was produced in Example 126 (126a) and the title compound was obtained.

Brown liquid

IR (film) $\nu_{max}$ 2942, 1699, 1602, 1497, 1421, 1236, 1118, 928, 697 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.88-2.04 (2H, m), 2.81-2.91 (2H, m), 3.29 (1H, t, J = 6.3 Hz), 3.37 (1H, t, J = 6.3 Hz), 3.48-3.72 (8H, m), 4.52 (2H, brs), 5.09 (1H, s), 5.14 (1H, s), 6.50-6.59 (3H, m), 7.13 (1H, m), 7.22-7.40 (10H, m);

MS (FAB) m/z: 444 [$M^+$], 386, 354, 266, 246, 165.

(126c) 2-[3-(1,4-diazepan-1-yl)phenyl]ethanol

Iodotrimethylsilane (4.8 mL, 33.7 mmol) was added to a methylene chloride (26 mL) solution of benzyl 4-{3-[2-(benzyloxy)ethyl]phenyl}-1,4-diazepane-1-carboxylate (2.30 g, 5.20 mmol) which was produced in Example 126 (126b) and the mixture was stirred at room temperature for 23 hours. Water (50 mL) was added to the reaction liquid and partitioned and the obtained aqueous layer was made basic by

adding potassium carbonate. The aqueous layer was extracted with methylene chloride/2-propanol (4:1) (50 mL) three times and the solvent was evaporated under reduced pressure after the extract was dried over sodium sulfate and the title compound was obtained (1.05 g, yield 92%).

Brown liquid

IR (film) $\nu_{max}$ 3310, 2935, 1601, 1497, 1363, 1176, 1047, 771, 696 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.84-1.94 (2H, m), 2.76-2.89 (4H, m), 3.03 (2H, t, J =5.5 Hz), 3.51-3.60 (4H, m), 3.85 (2H, t, J =5.9 Hz), 6.50-6.61 (3H, m), 7.16 (1H, t, J =8.2 Hz);

MS (EI) m/z: 220 [$M^+$], 190, 178, 164, 152, 150, 133, 118, 91, 77, 43.

(126d) 4-{4-[3-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) and using 2-[3-(1,4-diazepan-1-yl)phenyl]ethanol which was produced in Example 126 (126c) and the title compound was synthesized.

Brown powder

Mp 147-155°C;

IR (KBr) $\nu_{max}$ 2946, 2205, 1625, 1524, 1354, 1250, 1177, 1040, 774 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.87-2.00 (2H, m), 2.64 (2H, t, J = 7.0 Hz), 3.48-3.61 (4H, m), 3.67-3.78 (4H, m), 3.91-4.00 (2H, m), 4.57 (1H, brs), 6.40-6.51 (2H, m), 6.56-6.66 (2H, m), 7.05 (1H, t, J = 7.8 Hz), 7.37 (1H, d, J = 7.8 Hz), 12.54 (1H, brs);

MS (FAB) m/z: 355 [M+$H^+$], 273, 242, 226, 180.

(126e) 3-amino-4-{4-[3-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-{4-[3-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 126 (126d) and the title compound was synthesized.

Pale yellow powder

Mp 120-123°C;

IR (KBr) $\nu_{max}$ 3436, 3325, 3185, 2939, 1649, 1598, 1499, 1450, 1370, 1234, 1047, 941, 771 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 2.10-2.18 (2H, m), 2.65 (2H, t, J = 7.3 Hz), 3.16-3.24 (2H, m), 3.25-3.32 (2H, m), 3.50-3.61 (4H, m), 3.73-3.79 (2H, m), 4.57 (1H, brt), 6.47 (1H, d, J = 7.3 Hz), 6.57-6.63 (2H, m), 6.98 (2H, brs), 7.03-7.12 (4H, m), 8.40 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 412 [$M+H^+$], 395, 353, 273, 242, 165;

Anal. Calcd for $C_{21}H_{25}N_5O_2S \cdot 0.67H_2O$: C, 59.55; H, 6.27; N, 16.54. Found: C, 59.42; H, 6.21; N, 16.66.

(Example 127) 3-amino-4-{4-[4-(3-hydroxypropyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1005)

(127a) 3-(4-bromophenyl)propan-1-ol

Methyl chloroformate (1.9 mL, 24.1 mmol) was added dropwise to a tetrahydrofuran (80 mL) solution of triethylamine (3.4 mL, 24.1 mmol) and 3-(4-bromophenyl) propanoic acid (5.02 g, 21.9 mmol) at 0°C and the mixture was stirred at room temperature for one hour under nitrogen atmosphere. Insolubles were removed by filtration from the reaction liquid and an aqueous solution (40 mL) of sodium borohydride (1.24 g, 32.9 mmol) was added to the filtrate and the mixture was stirred at room temperature for two hours. Ethyl acetate (200 mL) was added to the reaction liquid and the organic layer was washed with a saturated saline

solution (200 mL) twice, and the solvent was evaporated under reduced pressure after drying over sodium sulfate and the title compound was obtained (4.36 g, yield 93%).

Colourless liquid

IR (film) $\nu_{max}$ 3353, 2942, 1711, 1489, 1072, 1012, 833, 796 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.83-1.90 (2H, m), 2.67 (2H, t, J = 7.8 Hz), 3.66 (2H, t, J = 6.3 Hz), 7.06 (2H, d, J = 8.2 Hz), 7.39 (2H, d, J = 8.2 Hz);

MS (EI) m/z: 214 [$M^+$], 196, 169, 117, 104, 91, 90, 77, 51, 50, 39.

(127b) 1-[3-(benzyloxy)propyl]-4-bromobenzene

N,N-dimethylformamide (20 mL) solution of 3-(4-bromophenyl)propan-1-ol (4.22 g, 19.6 mmol) which was produced in Example 127 (127a) was blended with sodium hydride (55% oily, 1.03 g, 23.5 mmol) at 0°C under nitrogen atmosphere and the mixture was stirred for 10 minutes. The reaction mixture was blended with benzyl bromide (2.3 mL, 23.5 mmol) and the mixture was stirred at room temperature for three hours. The reaction liquid was cooled to 0°C, and the resultant solution was blended with water (10 mL) and ether (50 mL) and partitioned. The organic layer was washed with water (50 mL) twice and the solvent was evaporated under reduced pressure after drying over sodium sulfate. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1) and the title compound was obtained (4.78 g, yield 80%).

Colourless liquid

IR (film) $\nu_{max}$ 2941, 2858, 2384, 1488, 1455, 1364, 1102, 1073, 1012, 736, 698 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.87-1.94 (2H, m), 2.67 (2H, t, J = 7.8 Hz), 3.47 (2H, t, J = 6.3 Hz), 4.50 (2H, s), 7.04 (2H, d, J = 8.6 Hz), 7.29-7.39 (7H, m);

MS (EI) m/z: 304 [$M^+$], 225, 213, 183, 169, 117, 104, 91, 65.

(127c) benzyl 4-{4-[3-(benzyloxy)propyl]phenyl}-1,4-diazepane-1-carboxylate

Reaction with benzyl 1-homopiperazinecarboxylate was performed following a method described in Example 117 (117a) using 1-[3-(benzyloxy)propyl]-4-bromobenzene which was produced in Example 127 (127b) and the title compound was obtained.

Pale yellow liquid

IR (film) $\nu_{max}$ 2940, 1700, 1616, 1519, 1422, 1228, 1118, 928, 737, 698 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.85-2.02 (4H, m), 2.60 (2H, t, J = 7.8 Hz), 3.30 (1H, t, J = 5.9 Hz), 3.37 (1H, t, J = 6.3 Hz), 3.48 (2H, t, J = 6.6 Hz), 3.50.3.57 (4H, m), 3.61-3.66 (2H, m), 4.49 (2H, s), 5.07 (1H, s), 5.12 (1H, s), 6.60 (2H, d, J = 8.6 Hz), 7.01 (2H, d, J = 8.6 Hz), 7.25-7.33 (5H, m);

MS (FAB) m/z: 459 $[M+H]^+$, 458, 368, 351, 260, 242, 219, 65.

(127d) 1-{4-[3-(benzyloxy)propyl]phenyl}-1,4-diazepane

An ethanol (70 mL) solution of benzyl 4-{4-[3-(benzyloxy)propyl]phenyl}-1,4-diazepane-1-carboxylate (3.62 g, 7.9 mmol) which was produced in Example 127 (127c) was blended with 5% palladium-carbon (3.36 g, 1.6 mmol) and the mixture was stirred under hydrogen atmosphere for five hours. The reaction liquid was filtered and the solvent was evaporated under reduced pressure and a crude title compound was obtained (2.42 g, yield 95%).

Colourless liquid

IR (film) $\nu_{max}$ 3335, 2936, 2855, 1616, 1519, 1364, 1189, 1102, 737, 698 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.86-1.93 (4H, m), 2.61 (2H, t, J = 7.8 Hz), 2.83 (2H, t, J = 4.7 Hz), 3.03 (2H, t, J = 5.5 Hz), 3.48-3.57 (6H, m), 4.51 (2H, s), 6.63 (2H, d, J = 8.2 Hz), 7.03 (2H, d, J = 8.2 Hz), 7.29-7.36 (5H, m);

MS (EI) m/z: 324 $[M^+]$, 282, 268, 254, 233, 204, 189, 176, 160, 146, 132, 118, 91, 70, 65, 43, 42.

(127e) 3-[4-(1,4-diazepan-1-yl)-phenyl]propan-1-ol

A methylene chloride (50 mL) solution of 1-{4-[3-(benzyloxy)propyl]phenyl}-1,4-diazepane (2.16 g, 6.7 mmol) which was produced in Example 127 (127d) was blended with iodotrimethylsilane (3.8 mL, 26.6 mmol) under nitrogen atmosphere and the mixture was stirred for 10 minutes. Water (100 mL) was added to the reaction liquid and the aqueous layer was washed with methylene chloride (100 mL) twice. 4M sodium carbonate aqueous solution (50 mL) was added to the aqueous layer and extracted with methylene chloride/isopropanol (4:1) (100 mL) three times. The solvent was evaporated under reduced pressure after the extract was dried over sodium sulfate and the title compound was obtained (1.32 g, yield 73%).

Pale brown liquid

IR (film) $\nu_{max}$ 3310, 2934, 1616, 1519, 1365, 1189, 1058, 800 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.83-1.90 (4H, m), 2.59 (2H, t, J = 7.8 Hz), 2.82 (2H, t, J = 5.9 Hz), 3.02 (2H, t, J = 5.5 Hz), 3.50-3.56 (4H, m), 3.67 (2H, t, J = 6.7 Hz), 6.62 (2H, d, J = 8.6 Hz), 7.03 (2H, d, J = 8.6 Hz);

MS (EI) m/z: 234 [$M^+$], 204, 192, 178, 160, 146, 130, 118, 117, 91, 90, 77, 43, 42.

(127f) 4-{4-[4-(3-hydroxypropyl)phenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) using 3-[4-(1,4-diazepan-1-yl)-phenyl]propan-1-ol which was produced in Example 127 (127e) and the title compound was synthesized.

Brown powder

Mp 184-186°C;

IR (KBr) $\nu_{max}$ 2935, 2206, 1626, 1518, 1252, 1039, 930 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.64 (2H, quint, J = 7.8 Hz), 1.91-1.96 (2H, m), 2.45 (2H, t, J = 7.8 Hz), 3.36-3.40 (2H, m), 3.50 (2H, t, J = 5.9 Hz), 3.69-3.73 (4H, m), 3.94-3.96 (2H, m), 4.39 (1H, t, J = 4.9 Hz), 6.44 (1H, d, J = 7.8 Hz), 6.69 (2H, d, J = 8.8 Hz), 6.93 (2H, d, J = 8.8 Hz), 7.36 (1H, d, J = 7.8 Hz), 12.53 (1H, brs);
MS (FAB) m/z: 369 $[M+H]^+$, 273, 257, 246, 176, 63.

(127 g) 3-amino-4-{4-[4-(3-hydroxypropyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-{4-[4-(3-hydroxypropyl)phenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 127 (127f) and the title compound was synthesized.
Pale brown powder
Mp 237-241°C;
IR (KBr) $\nu_{max}$ 3439, 3325, 3174, 2935, 1645, 1577, 1518, 1370, 1057, 938, 900, 826, 805, 479 $cm^{-1}$;
$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.66 (2H, quint, J = 7.3 Hz), 2.11-2.15 (2H, m), 2.47-2.50 (2H, m), 3.21 (2H, brs), 3.29 (2H, brs), 3.41 (2H, q, J = 6.8 Hz), 3.52 (2H, t, J = 5.9 Hz), 3.74 (2H, t, J = 4.4 Hz), 4.40 (1H, t, J = 4.9 Hz), 6.70 (2H, d, J = 8.3 Hz), 6.97 (2H, brs), 7.00 (2H, d, J = 8.3 Hz), 7.08 (1H, d, J = 5.4 Hz), 7.09 (2H, brs), 8.40 (1H, d, J = 5.4 Hz);
HRMS m/z calcd for $C_{22}H_{28}O_2N_5S$ 426.1964, found 426.1994;
MS (ESI) m/z: 426 $[M+H]^+$, 360;
Anal. Calcd for $C_{22}H_{27}N_5O_2S \cdot 0.3H_2O$: C, 61.32; H, 6.46; N, 16.25; S, 7.44. Found: C, 61.07; H, 6.38; N, 16.49; S, 7.52.

(Example 128) 3-amino-4-(4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-107)

(128a) benzyl 4-[4-(trifluoroacetyl)phenyl]-1,4-diazepane-1-carboxylate

The reaction was performed in a similar method as described in Example 59 (59a) using benzyl 1-homopiperazinecarboxylate and 2,2,2,4'-tetrafluoroacetophenone and the title compound (quantitatively) was obtained.

Slightly orange oil

IR (film) $\nu_{max}$ 2959, 1697, 1595, 1528, 1423, 1166 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.93-2.06 (2H, m), 3.33-3.38 (1H, m), 3.40-3.46 (1H, m), 3.60-3.74 (6H, m), 5.07 (1H, s), 5.13 (1H, s), 6.67-6.74 (2H, m), 7.25-7.37 (5H, m), 7.91-7.98 (2H, m);

MS (FAB) m/z: 407 $[M+H]^+$, 406, 315, 289.

(128b) 4-{4-[(benzyloxy)carbonyl]-1,4-diazepan-1-yl}benzoic acid

benzyl 4-[4-(trifluoroacetyl)phenyl]-1,4-diazepane-1-carboxylate (7.18 g, 17.7 mmol) which was produced in Example 128 (128a) was dissolved in N,N-dimethylformamide (35.4 mL) and was blended with 8N aqueous solution of sodium hydroxide (4.42 mL, 35.3 mmol) and heated and the mixture was stirred at 80°C for one hour. The reaction liquid was cooled, diluted with water (70 mL) and washed with ethyl acetate (70 mL). After the aqueous layer was made acidic with 1N hydrochloric acid and extracted with ethyl acetate (10 mLx3), the organic layers were combined and the solvent was evaporated under reduced pressure after drying over magnesium sulfate. The residual substance was blended with ether (50 mL) to be crystallized, separated by filtration, washed with ether and dried and 5.82 g of the title compound was obtained (yield 69%).

Colourless prism crystal

Mp 135-137°C;

IR (KBr) $\nu_{max}$ 3063, 2947, 2667, 2562, 1699, 1667, 1600, 1417 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.92-2.07 (2H, m), 3.30-3.36 (1H, m), 3.41 (1H, t, J = 5.9 Hz), 3.58-3.71 (6H, m), 5.08 (1H, s), 5.14 (1H, s), 6.63-6.72 (2H, m), 7.24-7.38 (5H, m), 7.91-7.99 (2H, m);

MS (EI) m/z: 354 $M^{+\cdot}$, 263, 202.

(128c) benzyl 4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepane-carboxylate

Synthesis was performed with reference to J. Org. Chem. (1990), 55, 6252-6259 by the following method. 1,1'-carbonyldiimidazole (3.89 g, 24 mmol) was added to a tetrahydrofuran (80 mL) solution of 4-{4-[(benzyloxy)carbonyl]-1,4-diazepan-1-yl}benzoic acid (7.09 g, 20 mmol) which was produced in Example 128 (128b) under ice-cooling and the mixture was stirred for 30 minutes. The reaction liquid was warmed to room temperature and was blended with a tetrahydrofuran solution (2.0M, 15 mL, 30 mmol) of dimethylamine and the mixture was stirred for 30 minutes. A saturated sodium hydrogen carbonate aqueous solution (150 mL) was added to the reaction liquid and extracted with ethyl acetate (100 mLx3). The organic layers were combined, washed with a saturated saline solution (50 mL) and dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residual substance was purified by silica gel column chromatography (eluent: ethyl acetate) and 7.63 g of the title compound was obtained (quantitative).

Pale yellow oil

IR (film) $\nu_{max}$ 3475, 2939, 1699, 1608, 1493, 1423, 1391 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.90-2.06 (2H, m), 3.07 (6H, s), 3.26-3.33 (1H, m), 3.34-3.41 (1H, m), 3.52-3.70 (6H, m), 5.10 (1H, s), 5.14 (1H, s), 6.59-6.71 (2H, m), 7.22-7.42 (7H, m);

MS (FAB) m/z: 382 $\{M+H\}^+$, 337, 246.

(128d) 4-(1,4-diazepan-1-yl)-N,N-dimethylbenzamide

10% palladium-carbon (water content: 53 wt%, 1.10 g) was added to an ethanol (11 ml) solution of benzyl 4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepane-carboxylate (1.10 g, 2.88 mmol) which was produced in Example 128 (128c) and the mixture was stirred under hydrogen atmosphere for one hour. The reaction liquid was filtered and after the catalyst was washed with ethanol, 671 mg of the title compound was obtained (yield 94%) by evaporating the solvent from the obtained filtrate under reduced pressure.

Colourless oil

IR (film) $\nu_{max}$ 3444, 3321, 2931, 1672, 1608, 1493, 1390 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.85-1.94 (2H, m), 2.79-2.85 (2H, m), 3.00-3.05 (2H, m), 3.07 (6H, m), 3.54-3.64 (4H, m), 6.66 (2H, d, J = 8.6 Hz), 7.36 (2H, d, J = 8.6 Hz);

MS (EI) m/z: 247 $M^{+}\cdot$, 203, 191, 160.

(128e) 4-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]-N,N-dimethyl benzamide

The reaction was performed following a method described in Example 121 (121c) using 4-(1,4-diazepan-1-yl)-N,N-dimethylbenzamide which was produced in Example 128 (128d) and the title compound was synthesized. Yield 24%.

Slightly brown powder

Mp 239-241°C;

IR (KBr) $\nu_{max}$ 3180, 3147, 3045, 2960, 2918, 2208, 1605, 1525, $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.92-2.00 (2H, m), 2.94 (6H, s), 3.54-3.61 (2H, m), 3.71-3.81 (4H, m), 3.95-4.01 (2H, m), 6.44 (1H, d, J = 7.8 Hz), 6.79 (2H, d, J = 8.8 Hz), 7.26 (2H, d, J = 8.8 Hz), 7.36 (2H, d, J = 7.8 Hz), 12.50 (1H, br.s);

MS (FAB) m/z: 382 $[M+H]^{+}$, 337, 273;

Anal. Calcd for $C_{20}H_{23}N_5OS\cdot 0.6H_2O$: C, 61.23; H, 6.22; N, 17.85; S, 8.17. Found: C, 61.32; H, 6.18; N, 17.95; S, 8.12.

(128f) 3-amino-4-(4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]-N,N-dimethyl benzamide which was produced in Example 128 (128e) and the title compound was synthesized. Yield 83%.

Slightly brown powder

Mp 159-161°C;

IR (KBr) $\nu_{max}$ 3437, 3327, 3187, 2930, 2847, 1606, 1497, 1387 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.11-2.20 (2H, m), 2.97 (6H, s), 3.16-3.34 (2H, m), 3.58 (2H, t, J = 6.3 Hz), 3.78-3.84 (2H, m), 6.76 (2H, d, J = 9.0 Hz), 6.97 (2H, br.s), 7.04-7.12 (3H, m), 7.28 (2H, d, J = 9.0 Hz), 8.38 (1H, d, J = 5.1 Hz);

MS (FAB) m/z: 439 $[M+H]^+$, 394, 273;

Anal. Calcd for $C_{22}H_{26}N_6O_2S \cdot 1.2H_2O$: C, 57.42; H, 6.22; N, 18.26; S, 6.97. Found: C, 57.17; H, 6.03; N, 18.45; S, 6.83.

(Example 129) 3-amino-4-{4-[4-(azetidin-1-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-940)

(129a) benzyl 4-[4-(azetidin-1-ylcarbonyl)phenyl]-1,4-diazepane-1-carboxylate

The reaction was performed following a method described in Example 128 (128c) using 4-{4-[(benzyloxy)carbonyl]-1,4-diazepan-1-yl}benzoic acid which was produced in Example 128 (128b) and azetidine and the title compound was (quantitatively) synthesized.

Slightly yellow oil

IR (film) $\nu_{max}$ 3459, 2952, 2886, 1698, 1605, 1428, 1234, 1175 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.90-2.06 (2H, m), 2.32 (2H, quint, J = 7.8 Hz), 3.31 (2H, t, J = 6.3 Hz), 3.35-3.41 (2H, m), 3.52-3.69 (6H, m), 4.13-4.42 (4H, m), 5.08 (1H, s), 5.13 (1H, s), 6.60-6.69 (2H, m), 7.24-7.38 (5H, m), 7.52-7.62 (2H, m);
MS (FAB) m/z: 394 $[M+H]^+$, 337, 258, 246.

(129b) 1-[4-(azetidin-1-ylcarbonyl)phenyl]-1,4-diazepane

The reaction was performed following a method described in Example 128 (128d) using benzyl 4-[4-(azetidin-1-ylcarbonyl)phenyl]-1,4-diazepane-1-carboxylate which was produced in Example 129 (129a) and azetidine and the title compound was synthesized (yield 98%).

Colourless oil

IR (film) $\nu_{max}$ 3416, 3321, 2941, 1606, 1433, 1406, 1177 $cm^{-1}$;
$^1$H NMR($CDCl_3$, 400 MHz) δ 1.89 (2H, quint, J = 5.9 Hz), 2.26-2.37 (2H, m), 2.78-2.86 (2H, m), 2.99-3.07 (2H, m), 3.53-3.66 (4H, m), 4.11-4.45 (4H, m), 6.65 (2H, d, J = 9.0 Hz), 7.56 (2H, d, J = 9.0 Hz);
MS (EI) m/z: 259 $M^{+\cdot}$, 217, 203, 189.

(129c) 4-{4-[4-(azetidin-1-ylcarbonyl)phenyl}-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) using 1-[4-(azetidin-1-ylcarbonyl)phenyl]-1,4-diazepane which was produced in Example 129 (129b) and azetidine and the title compound was synthesized.
Yield 25%.

White powder

Mp 136-138°C;

IR (KBr) $\nu_{max}$ 3441, 2950, 2882, 2204, 1605, 1522, 1432, 1402 $cm^{-1}$;
$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.90-1.99 (2H, m), 2.23 (2H, quint, J = 7.8 Hz), 3.59 (2H, t, J = 5.9 Hz), 3.72-3.83 (4H, m), 3.88-4.41 (6H, m), 6.44 (1H, d, J = 7.8

Hz), 6.79 (2H, d, J = 8.8 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.48 (2H, d, J = 8.8 Hz), 12.53 (1H, br.s);

MS (FAB) m/z: 394 $[M+H]^+$, 378, 337, 273;

Anal. Calcd for $C_{21}H_{23}N_5OS \cdot 0.84H_2O$: C, 61.72; H, 6.09; N, 17.14; S, 7.85. Found: C, 61.88; H, 5.82; N, 17.10; S, 7.74.

(129d) 3-amino-4-{4-[4-(azetidin-1-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-{4-[4-(azetidin-1-ylcarbonyl)phenyl}-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 129 (129c) and azetidine and the title compound was synthesized. Yield 77%.

Slightly brown powder

Mp 141-143°C;

IR (KBr) $\nu_{max}$ 3438, 3325, 3189, 2952, 2882, 1648, 1604, 1432, 1399, $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.10-2.30 (4H, m), 3.14-3.25 (2H, m), 3.26-3.38 (2H, m), 3.55-3.65 (2H, m), 3.79-3.88 (2H, m), 3.92-4.42 (4H, m), 6.79 (2H, d, J = 8.6 Hz), 6.98 (2H, br.s), 7.08 (1H, d, J = 5.5 Hz), 7.11 (2H, br.s), 7.50 (2H, d, J = 8.6 Hz), 8.40 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 451 $[M+H]^+$, 434, 394, 273;

Anal. Calcd for $C_{23}H_{26}N_6O_2S \cdot 1.2H_2O$: C, 58.81; H, 6.06; N, 17.80; S, 6.79. Found: C, 58.61; H, 6.00; N, 17.50; S, 6.64.

(Example 130) 3-amino-4-{4-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-970)

(130a) benzyl 4-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepane-1-carboxylate

The reaction was performed following a method described in Example 128 (128c) using 4-{4-[(benzyloxy)carbonyl]-1,4-diazepan-1-yl}benzoic acid which was

produced in Example 128 (128b) and morpholine and the title compound was synthesized (quantitative).

Slightly brown oil

IR (film) $\nu_{max}$ 3485, 2957, 2928, 2857, 1698, 1607, 1424 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.91-2.06 (2H, m), 3.31 (1H, t, J = 6.3 Hz), 3.38 (1H, t, J = 6.3 Hz), 3.54-3.74 (14H, m), 5.09 (1H, s), 5.13 (1H, s), 6.63-6.71 (2H, m), 7.28-7.39 (7H, m);

MS (FAB) m/z: 424 $[M+H]^+$, 337, 273.

(130b) 1-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepane

The reaction was performed following a method described in Example 128 (128d) using benzyl 4-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepane-1-carboxylate which was produced in Example 130 (130a) and the title compound was synthesized (quantitative).

Colourless oil

IR (film) $\nu_{max}$ 3417, 3314, 2929, 2855, 1607, 1524, 1457, 1431 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.89 (2H, q, J = 5.9 Hz), 2.78-2.86 (2H, m), 2.99-3.07 (2H, m), 3.53-3.77 (12H, m), 6.66 (2H, d, J = 9.0 Hz), 7.34 (2H, d, J = 9.0 Hz);

MS (EI) m/z: 289 $M^{+\cdot}$, 247, 233, 203.

(130c) 4-{4-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) using 1-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepane which was produced in Example 130 (130b) and the title compound was synthesized. Yield 46%.

Brown foam

IR (KBr) $\nu_{max}$ 3434, 3198, 3132, 2958, 2922, 2854, 2204, 1606, 1520 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 400 MHz) δ 2.07-2.16 (2H, m), 3.54-3.79 (12H, m), 3.82-3.89 (2H, m), 4.11-4.18 (2H, m), 6.20 (1H, d, J = 7.4 Hz), 6.70 (2H, d, J = 8.6 Hz), 7.23 (1H, d, J = 7.4 Hz), 7.36 (2H, d, J = 8.6 Hz), 11.57 (1H, br.s);
MS (FAB) m/z: 424 $[M+H]^+$, 337, 273.

(130d) 3-amino-4-{4-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-{4-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 130 (130c) and the title compound was synthesized. Yield 43%.
Slightly brown powder
Mp 274-275°C;
IR (KBr) $\nu_{max}$ 3437, 3323, 3189, 2957, 2921, 2852, 1606, 1367 $cm^{-1}$;
$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.12-2.20 (2H, m), 3.18-3.25 (2H, m), 3.27-3.35 (2H, m), 3.48-3.55 (4H, m), 3.57-3.64 (6H, m), 3.80-3.86 (2H, m), 6.80 (2H, d, J = 8.8 Hz), 6.96 (2H, br.s), 7.06-7.13 (3H, s), 7.29 (2H, d, J = 8.8 Hz), 8.41 (1H, d, J = 5.4 Hz);
MS (FAB) m/z: 481 $[M+H]^+$, 273, 258, 242;
Anal. Calcd for $C_{24}H_{28}N_6O_3S$: C, 59.98; H, 5.87; N, 17.49; S, 6.67. Found: C, 59.89; H, 5.89; N, 17.28; S, 6.70.

(Example 131) 3-amino-4-(4-{4-[2-(dimethylamino)-2-oxoethyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-925)

(131a) benzyl 4-{4-[2-(dimethylamino)-2-oxoethyl]phenyl}-1,4-diazepane-1-carboxylate

The reaction was performed following a method described in Example 117 (117a) using benzyl 1-homopiperazinecarboxylate in place of tert-butyl 1-piperazinecarboxylate and the title compound was obtained. Yield 80%.

Yellow oil

IR (film) $\nu_{max}$ 3481, 2939, 1699, 1642, 1520, 1423 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.90-2.06 (2H, m), 2.95 (3H, s), 3.00 (3H, s), 3.27-3.33 (1H, m), 3.34-3.40 (1H, m), 3.50-3.67 (8H, m), 5.08 (1H, s), 5.13 (1H, s), 6.60-6.68 (2H, m), 7.10 (2H, d, J = 8.2 Hz), 7.27-7.40 (5H, m);

MS (FAB) m/z: 396 $[M+H]^+$, 323, 260.

(131b) 2-[4-(1,4-diazepan-1-yl)phenyl]-N,N-dimethylacetamide

The reaction was performed following a method described in Example 128 (128d) using benzyl 4-{4-[2-(dimethylamino)-2-oxoethyl]phenyl}-1,4-diazepane-1-carboxylate which was produced in Example 131 (131a) and the title compound was obtained. Yield 94%.

Pale yellow oil

IR (film) $\nu_{max}$ 3430, 2934, 1629, 1520, 1398 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.88 (2H, quint, J = 5.9 Hz), 2.79-2.84 (2H, m), 2.94 (3H, s), 2.97-3.04 (5H, m), 3.47 (2H, s), 3.49-3.57 (4H, m), 6.62 (2H, d, J = 9.0 Hz), 7.07 (2H, d, J = 9.0 Hz);

MS (FAB) m/z: 262 $[M+H]^+$, 261, 219, 189.

(131c) 2-{4-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]phenyl}-N,N-dimethylacetamide

The reaction was performed following a method described in Example 121 (121c) using 2-[4-(1,4-diazepan-1-yl)phenyl]-N,N-dimethylacetamide which was produced in Example 131 (131b) and the title compound was synthesized (yield 47%).

Brown amorphous

IR (KBr) $\nu_{max}$ 3124, 3034, 2938, 2203, 1616, 1519 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 2.04-2.16 (2H, m), 2.96 (3H, s), 3.02 (3H, s), 3.52-3.63 (4H, m), 3.69-3.82 (4H, m), 4.08-4.16 (2H, m), 6.19 (1H, d, J = 7.8 Hz), 6.66 (2H, d, J = 8.6 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.22 (1H, d, J = 7.8 Hz), 11.94 (1H, br.s);

MS (FAB) m/z: 396 $[M+H]^+$, 350, 323, 262.

(131d) 3-amino-4-(4-{4-[2-(dimethylamino)-2-oxoethyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 2-{4-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]phenyl}-N,N-dimethylacetamide which was produced in Example 131 (131c) and the title compound was synthesized (yield 56%).

Slightly yellow powder

Mp 133-135°C;

IR (KBr) $\nu_{max}$ 3435, 3326, 3189, 2935, 2839, 1634, 1579, 1519 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 2.10-2.18 (2H, m), 2.82 (3H, s), 2.98 (3H, s), 3.15-3.23 (2H, m), 3.25-3.33 (2H, m), 3.49-3.56 (4H, m), 3.72-3.78 (2H, m), 6.71 (2H, d, J = 8.8 Hz), 7.00 (2H, br.s), 7.03 (2H, d, J = 8.8 Hz), 7.07 (1H, d, J = 5.4 Hz), 7.09 (2H, br.s), 8.39 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 453 $[M+H]^+$, 452, 436, 380;

Anal. Calcd for $C_{23}H_{28}N_6O_2S \cdot 1.16H_2O$: C, 58.35; H, 6.45; N, 17.75. Found: C, 58.10; H, 6.19; N, 18.03.

(Example 132)

3-amino-4-(4-{4-[3-(dimethylamino)-3-oxopropyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-927)

(132a) 3-(4-bromophenyl)-N,N-dimethylpropanamide

According to a method described in Example 128 (128c), the title compound was obtained (yield 99%) using 3-(4-bromophenyl)propionic acid.

Colourless oil

IR (neat) $\nu_{max}$ 1648, 1488, 1400, 1012, 816 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 2.58 (2H, t, J = 7.8 Hz), 2.92 (2H, t, J = 7.8 Hz), 2.93 (6H, s), 7.08 (2H, d, J = 8.5 Hz), 7.38 (2H, d, J = 8.5);

MS (EI) m/z: 255 [$M^+$], 169;

Anal. Calcd for $C_{11}H_{14}NOBr \cdot 0.1\ H_2O$: C, 51.22; H, 5.55; N, 5.43; Br, 30.98. Found: C, 51.03; H, 5.67; N, 5.48; Br, 31.18.

(132b) benzyl 4-{4-[3-(dimethylamino)-3-oxopropyl]phenyl}-1,4-diazepane-1-carboxylate

The reaction was performed following a method described in Example 117 (117a) using 3-(4-bromophenyl)-N,N-dimethylpropanamide which was produced in Example 132 (132a) and benzyl 1-homopiperazinecarboxylate and the title compound was obtained (yield 77%).

Slightly yellow oil

IR (film) $\nu_{max}$ 3550, 3488, 2939, 1699, 1645, 1519 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.90-2.04 (2H, m), 2.52-2.59 (2H, m), 2.81-2.88 (2H, m), 2.92 (3H, s), 2.93 (3H, s), 3.30 (1H, t, J = 6.3 Hz), 3.34-3.39 (1H, m), 3.49-3.59

(4H, m), 3.60-3.67 (2H, m), 5.07 (1H, s), 5.12 (1H, s), 6.58-6.64 (2H, m), 7.05 (2H, d, J = 8.2 Hz), 7.25-7.35 (5H, m);
MS (FAB) m/z: 410 $[M+H]^+$, 409, 323, 274.

(132c) 3-[4-(1,4-diazepan-1-yl)phenyl]-N,N-dimethylpropanamide

The title compound was obtained (quantitatively) by performing the reaction following a method described in Example 128 (128d) using benzyl 4-{4-[3-(dimethylamino)-3-oxopropyl]phenyl}-1,4-diazepane-1-carboxylate which was produced in Example 132 (132b).
Slightly yellow oil
IR (film) $\nu_{max}$ 3445, 3319, 2931, 1635, 1520 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.88 (2H, quint, J = 5.9 Hz), 2.53-2.60 (2H, m), 2.78-2.88 (4H, m), 2.93 (3H, s), 2.94 (3H, s), 2.98-3.03 (2H, m), 3.49-3.57 (4H, m), 6.61 (2H, d, J = 8.6 Hz), 7.04 (2H, d, J = 8.6 Hz);
MS (EI) m/z: 275 $M^{+\cdot}$, 233, 219.

(132d) 3-{4-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]phenyl}-N, N-dimethylpropanamide

The reaction was performed following a method described in Example 121 (121c) using 3-[4-(1,4-diazepan-1-yl)phenyl]-N,N-dimethylpropanamide which was produced in Example 132 (132c) and the title compound was synthesized. Yield 49%.
Brown foam
IR (KBr) $\nu_{max}$ 3124, 2932, 2204, 1732, 1615, 1518 $cm^{-1}$;
$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.06-2.14 (2H, m), 2.53-2.60 (2H, m), 2.81-2.88 (2H, m), 2.94 (6H, s), 3.51-3.57 (2H, m), 3.70-3.80 (4H, m), 4.08-4.13 (2H, m), 6.21

(1H, d, J = 7.8 Hz), 6.63 (2H, d, J = 8.6 Hz), 7.07 (2H, d, J = 8.6 Hz), 7.26 (1H, d, J = 7.8 Hz), 12.27 (1H, br.s);
MS (FAB) m/z: 410 $[M+H]^+$, 219, 176.

(132e) 3-amino-4-(4-{4-[3-(dimethylamino)-3-oxopropyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 3-{4-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]phenyl}-N, N-dimethylpropanamide which was produced in Example 132 (132d) and the title compound was synthesized. Yield 62%.
Slightly brown powder
Mp 241-243°C;
IR (KBr) $\nu_{max}$ 3445, 3328, 3173, 2941, 2840, 1637, 1578, 1518, 1368 $cm^{-1}$;
$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 2.06-2.16 (2H, m), 2.49-2.56 (2H, m), 2.63-2.70 (2H, m), 2.80 (3H, s), 2.93 (3H, s), 3.14-3.33 (4H, m), 3.48-3.54 (2H, m), 3.70-3.77 (2H, m), 6.67 (2H, d, J = 8.6 Hz), 6.93 (2H, br.s), 7.02 (2H, d, J = 8.6 Hz), 7.05 (1H, d, J = 5.5 Hz), 7.06 (2H, br.s), 8.37 (1H, d, J = 5.5 Hz);
MS (FAB) m/z: 467 $[M+H]^+$, 466, 394, 380;
Anal. Calcd for $C_{24}H_{30}N_6O_2S \cdot 0.3H_2O$: C, 61.07; H, 6.53; N, 17.80; S, 6.79. Found: C, 61.02; H, 6.42; N, 18.03; S, 6.74.

(Example 133) 3-amino-4-(4-{4-[2-(dimethylamino)ethyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-979)
(133a) N-{2-[4-(1,4-diazepan-1-yl)phenyl]ethyl}-N,N-dimethylamine

A tetrahydrofuran (20 mL) solution of 2-[4-(1,4-diazepan-1-yl)phenyl]-N,N-dimethylacetamide (1.32 g, 5.06 mmol) which was produced in Example 131 (131b) was slowly added dropwise to a tetrahydrofuran (5 mL) suspension of lithium

aluminum hydride (576 mg, 15.2 mmol) under ice-cooling. After the dropwise addition was completed, the reaction liquid was stirred at room temperature for one hour and tetrahydrofuran (25 mL) was added. The reaction liquid was ice-cooled and carefully blended with 1N aqueous solution of sodium hydroxide (2,880 μL) and the mixture was stirred at room temperature for 30 minutes. Subsequently anhydrous sodium sulfate was added, and after the mixture was stirred at room temperature for a further 30 minutes, insolubles were removed by Celite filtration. The insolubles were washed with tetrahydrofuran and the solvent was concentrated under reduced pressure from the collected filtrate. Toluene was added to the residual substance and the solvent was azeotropically distilled under reduced pressure and 1.16 g of the title compound was obtained (yield 92%).

Yellow oil

IR (film) $\nu_{max}$ 3315, 2938, 2858, 2818, 2778, 1616, 1520, 1461 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.88 (2H, quint, J = 5.9 Hz), 2.28 (6H, s), 2.44-2.50 (2H, m), 2.63-2.69 (2H, m), 2.79-2.84 (2H, m), 2.98-3.03 (2H, m), 3.48-3.57 (4H, m), 6.62 (2H, d, J = 8.6 Hz), 7.02 (2H, d, J = 8.6 Hz);

MS (EI) m/z: 247 $M^{+\cdot}$, 202, 189.

(133b) 3-amino-4-(4-{4-[2-(dimethylamino)ethyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

(2Z)-2-cyano-3-ethoxybut-2-enethioamide (J. Org. Chem. (1962), 27,2433-2439) (797 mg, 4.68 mmol) was added to N,N-dimethylformamide (9.36 mL) solution of N-{2-[4-(1,4-diazepan-1-yl)phenyl]ethyl}-N,N-dimethylamine (1.16 g, 4.68 mmol) which was produced in Example 133 (133a) and the resultant mixture was stirred at room temperature for 15 minutes. Subsequently N,N-dimethylformamide dimethylacetal (684 μL, 5.15 mmol) was added, the mixture was stirred for one hour and then heated and the mixture was stirred at 80°C for 30

minutes. After the reaction liquid was allowed to be cooled to room temperature, the resultant solution was blended with 2-chloroacetamide (526 mg, 5.62 mmol) and 8N-aqueous solution of sodium hydroxide (1.75 mL, 14.0 mmol) and the mixture was stirred at room temperature for two hours. Furthermore, water (9.36 mL) and ethanol (4.68 mL) were added and the mixture was stirred for 30 minutes and the deposited crystal was separated by filtration, washed with 50% ethanol aqueous solution and then dried and 297 mg of the title compound was obtained (yield 14%).

Yellow powder

Mp 200-203°C;

IR (KBr)$\nu_{max}$ 3442, 3328, 3164, 2939, 2824, 1650, 1578, 1518 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.05-2.23 (2H, m), 2.17 (6H, s), 2.34-2.41 (2H, m), 2.52-2.61 (2H, m), 3.13-3.35 (4H, m), 3.47-3.55 (2H, m), 3.70-3.77 (2H, m), 6.69 (2H, d, J = 8.6 Hz), 6.98 (2H, br.s), 7.02 (2H, d, J = 8.6 Hz), 7.07 (1H, d, J = 5.4 Hz), 7.09 (2H, br.s), 8.40 (2H, d, J = 5.4 Hz);

MS (FAB) m/z: 439 $[M+H]^+$, 273, 258, 242;

Anal. Calcd for $C_{23}H_{30}N_6OS$: C, 62.99; H, 6.89; N, 19.16; S, 7.31. Found: C, 62.59; H, 6.91; N, 19.04; S, 7.07.

(Example 134) 4-[4-(5-acetylpyridin-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-142)

(134a) tert-butyl 4-(5-acetylpyridin-2-yl)-1,4-diazepane-1-carboxylate

An N-butanol (18 mL) suspension of 5-acetyl-2-bromopyridine (Chem. Ber. (1992), 1169-1190) (1.12 g, 5.6 mmol), tert-butyl 1-homopiperazinecarboxylate (1.23 g, 6.2) and sodium carbonate (0.77 g, 7.3) was stirred under heat reflux for 11 hours.

Insolubles were removed by filtration, and the residue which was obtained by evaporating the solvent was partitioned with ethyl acetate (100 mL) and water (50

mL). The solvent was evaporated under reduced pressure after the organic layer was dried over sodium sulfate. Residue was purified by silica gel column chromatography (hexane/ethyl acetate =1:1) and 1.57 g of the title compound was obtained (yield 88%).

Mp 120-122°C;

IR (KBr) $\nu_{max}$ 1677, 1666, 1603, 1167 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.39 (4.5H, s), 1.43 (4.5H, s), 1.93-1.99 (2H, m), 2.49 (3H, s), 3.23-3.37 (2H, m), 3.55-3.59 (2H, m), 3.66-3.74 (2H, m), 3.82-3.87 (2H, m), 6.51 (1H, d, J = 9.0 Hz), 8.00 (1H, dd, J = 2.4, 9.0 Hz), 8.73 (1H, d, J = 2.4 Hz);

MS (EI) m/z: 319 [$M^+$], 163, 57;

Anal. Calcd for $C_{17}H_{25}N_3O_3$: C, 63.93; H, 7.89; N, 13.16. Found: C, 63.74; H, 7.91; N, 13.08.

(134b) 1-[6-(1,4-diazepan-1-yl)pyridin-3-yl]ethanone

4N hydrochloric acid-1,4-dioxane solution (10 mL) was added to 1,4-dioxane (25 mL) solution of tert-butyl 4-(5-acetylpyridin-2-yl)-1,4-diazepane-1-carboxylate (1.55 g, 4.9) which was produced in Example 134 (134a) and the mixture was stirred at room temperature for three hours. 1N aqueous solution of sodium hydroxide (20 mL) was added to the residue which was obtained by concentrating the reaction mixture under reduced pressure and the aqueous layer was extracted with methylene chloride (2x50 mL). 1.05 g (99%) of the title compound was obtained by evaporating the solvent under reduced pressure after the extract was dried over sodium sulfate.

IR (neat) $\nu_{max}$ 3324, 1663, 1597, 1285, 957, 813 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.63 (1H, br), 1.87-1.93 (2H, m), 2.50 (3H, s), 2.84-2.87 (2H, m), 3.03-3.06 (2H, m), 3.75-3.84 (4H, m), 6.52 (1H, d, J = 9.0 Hz), 8.01 (1H, dd, J = 2.0, 9.0 Hz), 8.76 (1H, d, J = 2.0 Hz);

MS (EI) m/z: 219 [$M^+$], 163, 149;

Anal. Calcd for $C_{12}H_{17}N_3O \cdot 0.36\ H_2O$: C, 63.84; H, 7.91; N, 18.61. Found: C, 64.04; H, 7.93; N, 18.25.

(134c) (2Z)-3-[4-(5-acetylpyridin-2-yl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide

The reaction was performed following a method described in Example 5 (5a) using 1-[6-(1,4-diazepan-1-yl)pyridin-3-yl]ethanone which was produced in Example 134 (134b) in place of isobutylamine and the title compound was synthesized.

Yield 87%.

Mp 184-187°C (dec.);

IR (KBr) $\nu_{max}$ 3298, 3178, 2180, 1661, 1655, 1597, 1273 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.89-1.95 (2H, m), 2.24 (3H, s), 2.45 (3H, s), 3.59-4.03 (8H, m), 6.83 (1H, d, J = 9.0 Hz), 7.97 (1H, dd, J = 2.0, 9.0 Hz), 8.41 (1H, br), 8.73 (1H, d, J = 2.0 Hz), 9.06 (1H, br);

MS (FAB) m/z: 344 $[M + H]^+$;

Anal. Calcd for $C_{17}H_{21}N_5SO \cdot 0.16\ H_2O$: C, 58.96; H, 6.20; N, 20.22; S, 9.26. Found: C, 59.28; H, 6.29; N, 19.89; S, 8.94.

(134d) 4-[4-(5-acetylpyridin-2-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

[(2Z)-3-[4-(5-acetylpyridin-2-yl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide (1.00 g, 3.4 mmol) which was produced in Example 134 (134c) and N,N-dimethylformamide dimethylacetal (0.49 g, 0.54 mL, 4.1 mmol) were dissolved in N,N-dimethylformamide (10 mL) and the resultant solution was stirred at room temperature for one hour. Furthermore, after reaction was conducted at 100°C for two hours, the reaction mixture was concentrated under reduced pressure. 1N

aqueous solution of sodium hydroxide (10 mL) and ethyl acetate (50 mL) were added to the residue and partitioned. The aqueous layer was neutralized by adding 1N hydrochloric acid (10 mL) and extracted with ethyl acetate (3x50 mL). The extract was dried over sodium sulfate and the solvent was evaporated under reduced pressure. Ethanol was added to the obtained residue and a crude product (0.23 g) of the title compound was obtained by separating the deposited solid by filtration and washing it with ethanol.

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.90-1.96 (2H, m), 2.44 (3H, s), 3.74-4.06 (8H, m), 6.45 (1H, d, J = 7.4 Hz), 6.84 (1H, d, J = 9.4 Hz), 7.35-7.38 (1H, m), 7.95 (1H, brd, J = 9.4 Hz), 8.41 (1H, br), 8.71 (1H, brs), 12.59 (1H, br).

(134e) 4-[4-(5-acetylpyridin-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide

The title compound was obtained by performing the reaction following a method described in Example 5 (5c) using a crude product of 4-[4-(5-acetylthien-2-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 134 (134d). Yield 10% from (2Z)-3-[4-(5-acetylpyridin-2-yl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide.

Mp >250°C;

IR (KBr) $\nu_{max}$ 3442, 3329, 3170, 1647, 1596, 1277 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 2.12-2.20 (2H, m), 2.46 (3H, s), 3.17-3.35 (4H, m), 3.78-3.84 (2H, m), 4.04-4.13 (2H, m), 6.78 (1H, d, J = 9.0 Hz), 6.98 (2H, br), 7.05 (1H, d, J = 5.5 Hz), 7.09 (2H, br), 7.97 (1H, dd, J = 2.4, 9.0 Hz), 8.37 (1H, d, J = 5.5 Hz), 8.72 (1H, d, J = 2.4 Hz);

MS (FAB) m/z: 411 $[M + H]^+$;

Anal. Calcd for $C_{17}H_{21}N_5SO \cdot 0.16\ H_2O$: C, 58.96; H, 6.20; N, 20.22; S, 9.26. Found: C, 59.28; H, 6.29; N, 19.89; S, 8.94.

(Example 135) 4-[4-(5-acetylthiophen-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1111)

(135a) 1-[5-(1,4-diazepan-1-yl)thiophen-2-yl]ethanone

After 2-acetyl-5-bromothiophene (1.03 g, 5 mmol) and homopiperazine (1.50 g, 15 mmol) was mixed in water (5 mL), the mixture was stirred under heat reflux for ten hours. 1N aqueous solution of sodium hydroxide (10 mL) was added to the reaction mixture and the resultant solution was extracted with methylene chloride (2x30 mL). After the extract was dried over sodium sulfate, crude crystal which was obtained by evaporating the solvent under reduced pressure was recrystallized from ethyl acetate (30 mL) and 0.80 g (71%) of the title compound was obtained.

Mp 130-132°C;

IR (KBr) $\nu_{max}$ 3322, 1599, 1497, 1328, 788 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 1.77 (1H, br), 1.90-1.96 (2H, m), 2.40 (3H, s), 2.87-2.90 (2H, m), 3.04-3.07 (2H, m), 3.53-3.62 (4H, m), 5.85 (1H, d, J = 4.3 Hz), 7.44 (1H, d, J = 4.3 Hz);

MS (EI) m/z: 224 [$M^+$], 182, 168;

Anal. Calcd for $C_{11}H_{16}N_2SO \cdot 0.2\ H_2O$: C, 57.97; H, 7.25; N, 12.29; S, 14.07. Found: C, 58.09; H, 7.31; N, 12.31; S, 13.86.

(135b) (2Z)-3-[4-(5-acetylthiophen-2-yl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide

The reaction was performed following a method described in Example 5 (5a) using 1-[5-(1,4-diazepan-1-yl)thiophen-2-yl]ethanone which was produced in Example 135 (135a) in place of isobutylamine and the title compound was obtained. Yield 62%.

Mp 183-185°C;

IR (KBr) $\nu_{max}$ 3331, 3288, 3171, 2186, 1601, 1536, 1493, 1440, 1100 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.95-2.02 (2H, m), 2.26 (3H, s), 2.31 (3H, s), 3.55-3.79 (8H, m), 6.13 (1H, d, J = 4.0 Hz), 7.65 (1H, d, J = 4.0 Hz), 8.48 (1H, br), 9.12 (1H, br);

MS (FAB) m/z: 349 $[M + H]^+$;

Anal. Calcd for $C_{16}H_{20}N_4S_2O \cdot 0.1\ H_2O$: C, 54.86; H, 5.81; N, 15.99; S, 18.31. Found: C, 54.75; H, 6.01; N, 15.76; S, 18.33.

(135c) 4-[4-(5-acetylthiophen-2-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-3-[4-(5-acetylthiophen-2-yl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide (0.65 g, 1.9 mmol) which was produced in Example 135 (135b) and N,N-dimethylformamide dimethylacetal (0.24 g, 0.27 mL, 2.1 mmol) were dissolved in N,N-dimethylformamide (6 mL) and the resultant solution was stirred at room temperature for one hour. Furthermore, the reaction mixture was cooled to room temperature after having reacted at 100°C for two hours. Ethyl acetate and water were added to the reaction liquid and the deposited solid was separated by filtration and a crude product (0.11 g) of the title compound was obtained by further washing the deposited solid with water and ethanol.

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.94-2.00 (2H, m), 2.28 (3H, s), 3.59-3.61 (2H, m), 3.73-3.75 (2H, m), 3.81-3.83 (2H, m), 4.01-4.04 (2H, m), 6.11 (1H, d, J = 4.7 Hz), 6.46 (1H, d, J = 7.4 Hz), 7.36-7.39 (1H, m), 7.59 (1H, d, J = 4.7 Hz).

(135d) 4-[4-(5-acetylthiophen-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide

The title compound was obtained by performing the reaction following a method described in Example 5 (5c) using a crude product of 4-[4-(5-acetylthiophen-

2-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 135 (135c). Yield 10% from (2Z)-3-[4-(5-acetylthiophene-2-yl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide.

Mp 239-241°C;

IR (KBr) $\nu_{max}$ 3439, 3326, 3188, 1646, 1580, 1486, 1448, 1093 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 2.17-2.23 (2H, m), 2.30 (3H, s), 3.18-3.24 (2H, m), 3.32-3.36 (2H, m), 3.56-3.60 (2H, m), 3.80-3.84 (2H, m), 6.07 (1H, d, J = 4.5 Hz), 6.99 (2H, br), 7.06 (1H, d, J = 5.5 Hz), 7.10 (2H, br), 7.64 (1H, d, J = 4.5 Hz), 8.40 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 416 $[M + H]^+$;

Anal. Calcd for $C_{19}H_{21}N_5S_2O_2 \cdot 2.3\ H_2O$: C, 49.94; H, 5.65; N, 15.33; S, 14.03.

Found: C, 50.05; H, 5.40; N, 15.46; S, 13.83.

(Example 136) 3-amino-4-(4-{4-[(dimethylamino)carbonyl]-1,3-thiazol-2-yl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1116)

(136a) tert-butyl 4-[(benzoylamino)carbonothioyl]-1,4-diazepane-1-carboxylate

Benzoyl isothiocyanate (1.6 mL, 12 mmol) was added to a tetrahydrofuran (20 mL) solution of tert-butyl 1,4-diazepane-1-carboxylate (1.97 mL, 10 mmol) and the resultant mixture was stirred for ten hours. The reaction liquid was concentrated, and the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate =1:1) and the title compound was obtained (3.46 g, yield 95%).

Pale red foam

IR (KBr) $\nu_{max}$ 3244, 2974, 1693, 1526, 1416, 1246, 1166, 709 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 500 MHz) δ 1.48 (9H, s), 2.09-2.17 (2H, m), 3.48-3.63 (4H, m), 3.79-3.88 (2H, m), 4.10-4.17 (2H, m), 7.49-7.51 (2H, m), 7.58-7.60 (1H, m), 7.84 (2H, d, J = 7.8 Hz), 8.26-8.29 (1H, m);

HRMS m/z calcd for $C_{18}H_{25}O_3N_3SNa$ 386.1514, found 386.1508;

MS (FAB) m/z: 364 $[M+H]^+$, 348, 332, 308, 274, 264, 246, 230, 214, 187, 165, 105, 93, 89, 77, 65, 57.

(136b) tert-butyl 4-(aminocarbonothioyl)-1,4-diazepane-1-carboxylate

Sodium methylate (4.9M methanol solution) (2.1 mL, 10.5 mmol) was added to methanol (50 mL) solution of tert-butyl 4-[(benzoylamino)carbonothioyl]-1,4-diazepane-1-carboxylate (3.46 g, 9.5 mmol) which was produced in Example (136a) and the resultant mixture was heated under reflux for two days. The reaction liquid was concentrated and the obtained residue was purified by silica gel column chromatography (ethyl acetate) and the title compound was obtained (2.52 g, yield 93%).

White foam

IR (KBr) $\nu_{max}$ 3370, 3199, 2976, 1681, 1641, 1492, 1420, 1365, 1168 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 500 MHz) δ 1.47 (9H, s), 1.96-1.99 (2H, m), 3.38-3.44 (2H, m), 3.57-3.61 (6H, m), 5.71 (2H, brs);

HRMS m/z calcd for $C_{11}H_{21}O_2N_3SNa$ 282.1252, found 282.1228;

MS (ESI) m/z: 282 $[M+Na]^+$, 260;

Anal. Calcd for $C_{11}H_{21}N_3O_2S$: C, 50.94; H, 8.16; N, 16.20; S, 12.36. Found: C, 51.01; H, 8.18; N, 16.02, S, 12.21.

(136c) tert-butyl 4-[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]-1,4-diazepane-1-carboxylate

Triethylamine (2.2 mL, 15.8 mmol) and ethyl bromopyruvate (2.0 mL, 15.8 mmol) were added to an ethanol (20 mL) solution of tert-butyl 4-(aminocarbonothioyl)-1,4-diazepane-1-carboxylate (2.04 g, 7.9 mmol) which was produced in Example (136b) and the resultant mixture was heated under reflux for 30 minutes. The reaction liquid was concentrated, and the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) and the title compound was obtained (2.80 g, yield 99%).

Pale yellow liquid

IR (film) $\nu_{max}$ 2978, 1695, 1550, 1416, 1368, 1212, 1168 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$1.36 (3H, t, J = 7.3 Hz), 1.43 (4.5H, s), 1.44 (4.5H, s), 2.01 (2H, quint, J = 5.9 Hz), 3.35 (1H, t, J = 5.9 Hz), 3.43 (1H, t, J = 4.4 Hz), 3.61-3.77 (6H, m), 4.34 (2H, q, J = 7.3 Hz), 7.38 (1H, s);

MS (FAB) m/z: 356 $[M+H]^+$, 273, 242, 226, 165, 65.

(136d) tert-butyl 4-{4-[(dimethylamino)carbonyl]-1,3-thiazol-2-yl]-1,4-diazepane-1-carboxylate

Trimethylaluminum (2.0M toluene solution, 7.9 mL, 15.8 mmol) was added dropwise to a toluene (16 mL) solution of dimethylamine hydrochloride (1.28 g, 15.8 mmol) under nitrogen atmosphere and the resultant mixture was stirred for two hours. The above dimethylaluminum amide solution was added dropwise to a toluene (80 mL) solution of tert-butyl 4-[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]-1,4-diazepane-1-carboxylate (2.80 g, 7.9 mmol) which was produced in Example (136c) and the resultant solution was heated under reflux for 50 minutes. An ammonium chloride aqueous solution (50 mL) and ethyl acetate (50 mL) were added to the reaction liquid and the resultant solution was filtered with Celite. The obtained filtrate was extracted with ethyl acetate (50 mL) twice and the solvent was evaporated under reduced pressure after drying the extract over sodium sulfate. The obtained residue was

purified by silica gel column chromatography (hexane/ethyl acetate =1:1) and the title compound was obtained (1.69 g, yield 60%).

Pale yellow liquid

IR (film) $\nu_{max}$ 3492, 2932, 1693, 1626, 1546, 1414, 1169 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.44 (9H, s), 2.00 (2H, quint, J = 5.9 Hz), 3.06 (3H, brs), 3.24 (3H, brs), 3.33 (1H, t, J = 5.9 Hz), 3.42 (1H, t, J = 5.9 Hz), 3.57-3.68 (6H, m), 7.02 (1H, s);

MS (FAB) m/z: 355 $[M+H]^+$, 255, 242, 210, 57.

(136e) 2-(1,4-diazepan-1-yl)-N,N-dimethyl-1,3-thiazole-4-carboxamide

The reaction was performed following a method described in Example 57 (57b) using tert-butyl 4-{4-[(dimethylamino)carbonyl]-1,3-thiazol-2-yl}-1,4-diazepane-1-carboxylate which was produced in Example 136 (136d) and the title compound was obtained.

Pale yellow liquid

IR (film) $\nu_{max}$ 3442, 2936, 1618, 1548, 1453, 1398, 1319, 1175, 719 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.93 (2H, quint, J = 5.9 Hz), 2.90 (2H, t, J = 5.9 Hz), 3.04-3.06 (5H, m), 3.25 (3H, brs), 3.65-3.69 (4H, m), 6.99 (1H, s);

MS (EI) m/z: 254 $[M^+]$, 211, 198, 185, 172, 167, 139, 128, 112, 83, 70, 56, 44.

(136f) 2-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]-N,N-dimethyl-1,3-thiazole-4-carboxamide

The reaction was performed following a method described in Example 118 (118c) using 2-(1,4-diazepan-1-yl)-N,N-dimethyl-1,3-thiazole-4-carboxamide which was produced in Example 136 (136e) and the title compound was synthesized.

Brown foam

IR (KBr) $\nu_{max}$ 2929, 1621, 1543, 1236, 1174, 1141, 922, 777 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 2.17 (2H, quint, J = 5.4 Hz), 3.07 (3H, brs), 3.21 (3H, brs), 3.67 (2H, t, J = 6.3 Hz), 3.86 (2H, t, J = 5.9 Hz), 3.96 (2H, t, J = 5.4 Hz), 4.14 (2H, t, J = 4.9 Hz), 6.25 (1H, d, J = 7.8 Hz), 7.05 (1H, s), 7.33 (1H, d, J = 7.8 Hz), 12.35 (1H, brs);
MS (FAB) m/z: 389 $[M+H]^+$, 273, 242, 226, 1665, 65.

(136 g) 3-amino-4-(4-{4-[(dimethylamino)carbonyl]-1,3-thiazol-2-yl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 2-[4-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]-N,N-dimethyl-1,3-thiazole-4-carboxamide which was produced in Example 136 (136f) and the title compound was synthesized.
White powder
Mp 285-287°C(dec.);
IR (KBr) $\nu_{max}$ 3441, 3326, 3165, 1669, 1603, 1532, 1370, 1174, 922, 664, 628 $cm^{-1}$;
$^1$H NMR(DMSO-$d_6$, 400 MHz) δ 2.20-2.22 (2H, m), 2.93 (3H, brs), 3.12 (3H, brs), 3.24 (2H, brs), 3.38 (2H, brs), 3.65 (2H, t, J = 6.3 Hz), 3.94-3.96 (2H, m), 7.03 (2H, brs), 7.08-7.10 (2H, m), 7.12 (2H, brs), 8.42 (1H, d, J = 5.5 Hz);
HRMS m/z calcd for $C_{19}H_{24}O_2N_7S_2$ 446.1433, found 446.1409;
MS (ESI) m/z: 446 $[M+H]^+$, 429;
Anal. Calcd for $C_{19}H_{23}N_7O_2S_2 \cdot 0.6H_2O$: C, 50.00; H, 5.34; N, 21.48. Found: C, 50.01; H, 5.38; N, 21.37.

(Example 137) 4-[4-(4-acetyl-1,3-thiazol-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1110)
(137a) tert-butyl 4-(4-acetyl-1,3-thiazol-2-yl)-1,4-diazepane-1-carboxylate

Methyl magnesium chloride (3M tetrahydrofuran solution) (1.2 mL, 3.6 mmol) was added dropwise to a tetrahydrofuran (25 mL) solution of tert-butyl 4-{4-[(dimethylamino)carbonyl]-1,3-thiazol-2-yl}-1,4-diazepan-1-carboxylate (1.05 g, 3.0 mmol) which was produced in Example 136 (136d) at 0°C and the resultant solution was stirred for three hours. An ammonium chloride aqueous solution (30 mL) was added to the reaction liquid and the resultant solution was extracted with ethyl acetate (50 mL) twice, and the solvent was evaporated under reduced pressure after drying the extract over sodium sulfate. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1) and the title compound was obtained (0.66 g, yield 69%).

Colourless liquid

IR (film) $\nu_{max}$ 2975, 1687, 1549, 1416, 1167, 927, 606 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.43 (4.5H, s), 1.44 (4.5H, s), 2.01 (2H, quint, J = 6.4 Hz), 2.53 (3H, s), 3.35 (1H, t, J = 5.9 Hz), 3.43 (1H, t, J = 4.9 Hz), 3.63-3.71 (6H, m), 7.35 (1H, s);

MS (FAB) m/z: 326 $[M+H]^+$, 270, 252, 224, 169, 57.

(137b) 1-[2-(1,4-diazepan-1-yl)-1,3-thiazol-4-yl]ethanone

The reaction was performed following a method described in Example 57 (57b) using tert-butyl 4-(4-acetyl-1,3-thiazol-2-yl)-1,4-diazepane-1-carboxylate which was produced in Example 137 (137a) and the title compound was synthesized.

Yellow liquid

IR (film) $\nu_{max}$ 3329, 2938, 1679, 1550, 1355, 1211, 915, 695, 605 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.94 (2H, quint, J = 4.9 Hz), 2.54 (3H, s), 2.92 (2H, t, J = 5.5 Hz), 3.07 (2H, t, J = 5.5 Hz), 3.69-3.73 (4H, m), 7.34 (1H, s);

MS (EI) m/z: 225 $[M^+]$, 210, 197, 183, 169, 155, 141, 128, 83, 70, 56, 43.

(137c) 4-[4-(4-acetyl-1,3-thiazol-2-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) using 1-[2-(1,4-diazepan-1-yl)-1,3-thiazol-4-yl]ethanone which was produced in Example 137 (137b) and the title compound was synthesized.

Brown solid

IR (KBr) $\nu_{max}$ 3097, 2959, 2204, 1672, 1623, 1545, 1354, 1242, 1143, 924, 776, 604 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.96-2.01 (2H, m), 2.42 (3H, s), 3.68 (2H, t, J = 5.9 Hz), 3.84-3.88 (4H, m), 4.09 (2H, t, J = 5.4 Hz), 6.47 (1H, d, J = 7.8 Hz), 7.38 (1H, d, J = 7.8 Hz), 7.64 (1H, s), 12.54 (1H, brs);

MS (FAB) m/z: 360 $[M+H]^+$, 344, 328, 273, 242, 226, 165, 65;

Anal. Calcd for $C_{16}H_{17}N_5OS_2 \cdot 0.33H_2O$: C, 52.58; H, 4.87; N, 19.16; S, 17.55. Found: C, 52.38; H, 4.68; N, 19.37; S, 17.48.

(137d) 4-[4-(4-acetyl-1,3-thiazol-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-[4-(4-acetyl-1,3-thiazol-2-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 137 (137c) and the title compound was synthesized.

Pale yellow powder

Mp 217-219°C;

IR (KBr) $\nu_{max}$ 3427, 3318, 3172, 1673, 1581, 1543, 1365, 1211, 937, 602 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.19-2.24 (2H, m), 2.45 (3H, s), 3.23 (2H, brs), 3.39 (2H, brs), 3.67 (2H, t, J = 5.9 Hz), 3.97 (2H, brs), 7.01 (2H, brs), 7.08 (1H, d, J = 5.5 Hz), 7.11 (2H, brs), 7.66 (1H, s), 8.04 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{18}H_{21}O_2N_6S_2$ 417.1167, found 417.1173;

MS (ESI) m/z: 417 $[M+H]^+$, 400;

Anal. Calcd for $C_{18}H_{20}N_6O_2S_2 \cdot 0.33H_2O$: C, 51.17; H, 4.93; N, 19.89; S, 15.18.

Found: C, 51.18; H, 4.85; N, 20.16; S, 14.83.

(Example 138) 3-amino-4-[4-(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1098)

(138a) ethyl 4-bromo-2-methylbenzoate

4N hydrochloric acid-1,4-dioxane solution was added to an ethanol solution of 4-bromo 2-methyl-benzoic acid (4.30 g, 20.0 mmol) and the resultant solution was stirred at 80°C for nine hours. The reaction liquid was concentrated and methylene chloride (200 mL) was added to the obtained residual substance and the resultant mixture was washed with 1N aqueous solution of sodium hydroxide (50 mL) and a saturated sodium chloride aqueous solution (50 mL), and the solvent was evaporated under reduced pressure after drying the extract over sodium sulfate and the title compound was obtained (4.54 g, yield 93%).

Yellow liquid

IR (film) $\nu_{max}$ 2981, 1722, 1589, 1445, 1253, 1082, 863, 771 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.38 (3H, t, J = 7.8 Hz), 2.57 (3H, s), 4.34 (2H, q, J = 7.8 Hz), 7.37 (1H, d, J = 8.2 Hz), 7.40 (1H, s), 7.77 (1H, d, J = 8.2 Hz);

MS (EI) m/z: 242 $[M^+]$, 199, 197, 171, 169, 163, 90, 63.

(138b) ethyl 4-bromo-2-(bromomethyl)benzoate

N-bromosuccinimide (3.62 g, 20.0 mmol), 2,2'-azobis (isobutyronitrile) (608 mg, 3.70 mmol) were sequentially added to carbon tetrachloride (90 ml) solution of ethyl 4-bromo-2-methylbenzoate (4.50 g, 18.5 mmol) which was produced in

Example 138 (138a) and the resultant mixture was stirred at 90°C for three hours. The reaction liquid was concentrated and hexane was added to the obtained residual substance and the resultant mixture was filtered. The filtrate was concentrated and a crude title compound was obtained (5.90 g, yield 99%).
Yellow liquid

(138c) 5-bromo-2-methylisoindolin-1-one

2M methylamine methanol solution was added to ethyl 4 -bromo-2-(bromomethyl)benzoate (5.62 g, 17.5 mmol) which was produced in Example 138 (138b) and the resultant mixture was stirred at 70°C for 23 hours. The reaction liquid was concentrated and the obtained residual substance was purified by silica gel column chromatography (hexane/ethyl acetate =1:2 to 1:4) and the title compound was obtained (2.70 g, yield 68%).
White powder
Mp 132-134°C;
IR (KBr) $\nu_{max}$ 2914, 1680, 1400, 1275, 1043, 769 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 3.19 (3H, s), 4.36 (2H, s), 7.58-7.63 (2H, m), 7.70 (1H, d, J = 8.6 Hz);
MS (EI) m/z: 225 [$M^+$], 199, 198, 197, 196, 171, 169, 146, 112, 98, 89, 75, 59;
Anal. Calcd for $C_9H_8BrNO$: C, 47.82; H, 3.57; N, 6.20. Found: C, 47.80; H, 3.59; N, 6.22.

(138d) benzyl 4-(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-1,4-diazepane-1-carboxylate

The reaction was performed following a method described in Example 117 (117a) using 5-bromo-2-methylisoindolin-1-one which was produced in Example

138 (138c) and benzyl 1-homopiperazinecarboxylate and the title compound was synthesized.

Pale yellow liquid

IR (film) $\nu_{max}$ 3451, 2947, 1679, 1479, 1239, 1120, 927, 754 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.93-2.05 (2H, m), 3.14 (3H, s), 3.33 (1H, t, J = 5.9 Hz), 3.41 (1H, t, J = 5.9 Hz), 3.58-3.70 (6H, m), 4.21 (1H, s), 4.26 (1H, m), 5.05 (1H, s), 5.13 (1H, s), 6.64 (1H, m), 6.73 (1H, m), 7.26-7.86 (5H, m), 7.65 (1H, m);

MS (FAB) m/z: 380 [$M+H^+$], 379, 353, 273, 246, 244.

(138e) 5-(1,4-diazepan-1-yl)-2-methylisoindoline-1-one

Hydrogenolysis reaction was performed using benzyl 4-(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-1,4-diazepane-1-carboxylate which was produced in Example 138 (138d) following a method described in Example 128 (128d) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 3421, 1658, 1480, 1399, 1250, 1111, 768 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.85-1.96 (2H, m), 2.83 (2H, t, J = 5.9 Hz), 3.05 (2H, t, J = 5.5 Hz), 3.14 (3H, s), 3.60 (2H, t, J = 5.5 Hz), 3.64 (2H, t, J = 5.9 Hz), 4.27 (2H, s), 6.65 (1H, s), 6.74 (1H, d, J = 8.6 Hz), 7.64 (1H, d, J = 8.6 Hz);

MS (EI) m/z: 245 [$M^+$], 203, 189, 177, 146, 83, 70.

(138f) 4-[4-(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) using 5-(1,4-diazepan-1-yl)-2-methylisoindolin-1-one which was produced in Example 138 (138e) and the title compound was synthesized.

Brown powder

Mp 257-265°C;

IR (KBr) $\nu_{max}$ 2950, 2203, 1660, 1615, 1522, 1246, 926, 767 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.93-2.00 (2H, m), 3.31 (3H, s), 3.62 (2H, t, J = 5.9 Hz), 3.75 (2H, t, J = 5.9 Hz), 3.82 (2H, t, J = 5.4 Hz), 4.00 (2H, t, J = 5.4 Hz), 4.31 (2H, s), 6.44 (1H, d, J = 7.8 Hz), 6.86 (1H, d, J = 8.8 Hz), 6.92 (1H, s), 7.36 (1H, d, J = 7.8 Hz), 7.41 (1H, d, J = 8.8 Hz), 12.55 (1H, brs);

MS (FAB) m/z: 380 [$M+H^+$], 273, 257, 238, 165, 85, 63;

Anal. Calcd for $C_{20}H_{21}N_5OS \cdot 1.75H_2O$: C, 58.45; H, 6.01; N, 17.04. Found: C, 58.21; H, 5.66; N, 16.82.

(138 g) 3-amino-4-[4-(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-[4-(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 138 (138f) and the title compound was synthesized.

Pale yellow powder

Mp 293-295°C;

IR (KBr) $\nu_{max}$ 3442, 3324, 3171, 2918, 1653, 1503, 1366, 1235, 1110, 767 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.13-2.24 (2H, m), 3.00 (3H, s), 3.14-3.24 (2H, m), 3.28-3.33 (2H, m), 3.63 (2H, t, J = 6.4 Hz), 3.85 (2H, t, J = 4.4 Hz), 4.32 (2H, s), 6.86 (1H, d, J = 8.8 Hz), 6.90 (1H, s), 7.01 (2H, brs), 7.07 (1H, d, J = 5.4 Hz), 7.11 (2H, brs), 7.44 (1H, d, J = 8.8 Hz), 8.40 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 437 [$M+H^+$], 420, 273, 246, 165, 93, 63;

Anal. Calcd for $C_{22}H_{24}N_6O_2S \cdot 0.67H_2O$: C, 58.91; H, 5.69; N, 18.74. Found: C, 58.83; H, 5.65; N, 18.74.

(Example 139) 3-amino-4-[4-(1,3-benzoxazol-6-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1099)

(139a) tert-butyl 4-(3-hydroxy-4-nitrophenyl)-1,4-diazepane-1-carboxylate

The reaction was performed following a method described in Example 59 (59a) using 5-fluoro-2-nitrophenol and tert-butyl 1-homopiperazinecarboxylate and the title compound was synthesized.

Yellow powder

Mp 106-109°C;

IR (KBr) $\nu_{max}$ 3431, 2973, 1690, 1625, 1566, 1415, 1325, 1262, 1166, 927, 754 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.39 (4.5H, s), 1.43 (4.5H, s), 1.95-1.99 (2H, m), 3.27 (1H, t, J = 5.9 Hz), 3.37 (1H, t, J = 5.9 Hz), 3.57-3.68 (6H, m), 6.18 (1H, brs), 6.31 (1H, brd, J = 9.3 Hz), 7.95 (1H, d, J = 9.3 Hz), 11.31 (1H, brs);

MS (EI) m/z: 337 [$M^+$], 280, 264, 236, 220, 193, 181, 70, 57;

Anal. Calcd for $C_{16}H_{23}N_3O_5$: C, 56.96; H, 6.87; N, 12.46. Found: C, 56.97; H, 6.85; N, 12.39.

(139b) tert-butyl 4-(1,3-benzoxazol-6-yl)-1,4-diazepane-1-carboxylate

Trimethyl orthoformate (80 mL), 10% palladium-carbon (5.2 g) were sequentially added to an ethanol (80 mL) solution of tert-butyl 4-(3-hydroxy-4-nitrophenyl)-1,4-diazepane-1-carboxylate (5.20 g, 15.4 mmol) which was produced in Example 139 (139a) and the resultant mixture was stirred under normal pressure hydrogen atmosphere at room temperature for five hours and then stirred at 90°C for 17 hours. The reaction mixture was filtered with Celite and the filtrate was concentrated. The obtained residual substance was purified by silica gel column chromatography (hexane/ethyl acetate =2:1 to 1:1 with one) and the title compound was obtained (611 mg, yield 13%).

Yellow liquid

IR (film) $\nu_{max}$ 2974, 1688, 1630, 1500, 1416, 1246, 1168, 1057, 929 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.32 (4.5H, s), 1.42 (4.5H, s), 1.96-2.04 (2H, m), 3.21 (1H, t, J = 5.9 Hz), 3.33 (1H, t, J = 5.9 Hz), 3.57-3.65 (6H, m), 6.77 (1H, dd, J = 2.0, 8.8 Hz), 6.82 (1H, brs), 7.57 (1H, d, J = 8.8 Hz), 7.87 (1H, s);
MS (FAB) m/z: 317 [$M^+$], 262, 242, 216, 165, 63.

(139c) 6-(1,4-diazepan-1-yl)-1,3-benzoxazole

A methylene chloride (10 mL) solution of tert-butyl 4-(1,3-benzoxazol-6-yl)-1,4-diazepane-1-carboxylate (534 mg, 1.68 mmol) which was produced in Example 139 (139b) was cooled to 0°C and was sequentially blended with 2,6-lutidine (0.5 mL, 4.30 mmol), trimethylsilyl trifluoromethanesulfonate (0.5 mL, 2.76 mmol) and the resultant mixture was stirred at 0°C for one hour. The reaction liquid was concentrated and the obtained residual substance was purified by silica gel column chromatography (methylene chloride/methanol =1:0 to 20:1) and the title compound was obtained (267 mg, yield 73%).
Yellow liquid
IR (film) $\nu_{max}$ 3396, 2932, 1624, 1510, 1358, 1176, 925 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.91-1.97 (2H, m), 2.84 (2H, t, J = 5.9 Hz), 3.07 (2H, t, J = 5.4 Hz), 3.60 (2H, t, J = 5.4 Hz), 3.64 (2H, t, J = 6.3 Hz), 6.77 (1H, dd, J = 2.0, 8.6 Hz), 6.82 (1H, d, J = 2.0 Hz), 7.57 (1H, d, J = 8.6 Hz), 7.87 (1H, s);
MS (FAB) m/z: 218 [$M+H^+$], 161, 63.

(139d) (2Z)-3-[4-(1,3-benzoxazol-6-yl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide

The reaction was performed following a method described in Example 5 (5a) using 6-(1,4-diazepan-1-yl)-1,3-benzoxazole which was produced in Example 139 (139c) in place of isobutylamine and the title compound was obtained.

Yellow powder

Mp 177-180°C;

IR (KBr) $\nu_{max}$ 3288, 3170, 2182, 1627, 1517, 1442, 1358, 1289, 1208, 1060, 876, 801 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.95-2.01 (2H, m), 2.24 (3H, s), 3.53 (2H, t, J = 5.4 Hz), 3.62 (2H, t, J = 5.9 Hz), 3.66 (2H, t, J = 5.4 Hz), 3.81 (2H, t, J = 5.9 Hz), 6.88 (1H, dd, J = 2.0, 8.8 Hz), 7.11 (1H, d, J = 2.0 Hz), 7.54 (1H, d, J = 8.8 Hz), 8.37 (1H, brs), 8.41 (1H, s), 9.02 (1H, brs);

MS (FAB) m/z: 342 [$M+H^+$], 326, 273, 258, 242, 226, 180, 165, 63;

Anal. Calcd for $C_{17}H_{19}N_5OS \cdot 0.30H_2O$: C, 58.91; H, 5.69; N, 20.21. Found: C, 59.26; H, 5.56; N, 19.92.

(139e) 4-[4-(1,3-benzoxazol-6-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 116 (116d) using (2Z)-3-[4-(1,3-benzoxazol-6-yl)-1,4-diazepan-1-yl]-2-cyanobut-2-enethioamide which was produced in Example 139 (139d) and the title compound was obtained.

Brown powder

Mp 245-250°C;

IR (KBr) $\nu_{max}$ 3119, 2955, 2204, 1625, 1517, 1354, 1252, 1062, 928, 803 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.94-2.02 (2H, m), 3.61 (2H, t, J = 5.9 Hz), 3.73 (2H, t, J = 5.5 Hz), 3.81 (2H, m), 4.00 (2H, t, J = 5.5 Hz), 6.44 (1H, d, J = 7.8 Hz), 6.89 (1H, d, J = 8.6 Hz), 7.13 (1H, brs), 7.36 (1H, d, J = 7.8 Hz), 7.53 (1H, d, J = 8.6 Hz),8.41 (1H, s), 12.53 (1H, brs);

MS (FAB) m/z: 352 [$M+H^+$], 273, 258, 242, 226, 165, 83, 63;

Anal. Calcd for $C_{18}H_{17}N_5OS \cdot 0.56H_2O$: C, 59.82; H, 5.05; N, 19.38. Found: C, 59.49; H, 4.76; N, 19.86.

(139f) 3-amino-4-[4-(1,3-benzoxazol-6-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-[4-(1,3-benzoxazol-6-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile of Example 139 (139e) and the title compound was obtained.

Pale yellow powder

Mp 159-162°C;

IR (KBr) $\nu_{max}$ 3441, 3323, 2948, 1643, 1580, 1500, 1455, 1368, 1204, 1058, 942, 803 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 2.14-2.22 (2H, m), 3.16-3.23 (2H, m), 3.29-3.36 (2H, m), 3.62 (2H, t, J = 5.9 Hz), 3.84 (2H, t, J = 4.4 Hz), 6.89 (1H, dd, J = 2.4, 8.8 Hz), 7.00 (2H, brs), 7.06-7.09 (4H, m), 7.55 (1H, t, J = 8.8 Hz), 8.40 (1H, d, J = 5.4 Hz), 8.41 (1H, s);

MS (FAB) m/z: 409 [$M+H^+$], 273, 258, 242, 226, 213, 180, 165, 63;

Anal. Calcd for $C_{20}H_{20}N_6O_2S \cdot 0.40H_2O$: C, 57.79; H, 5.04; N, 20.22. Found: C, 57.69; H, 4.79; N, 20.40.

(Example 140) 3-amino-4-[4-(4-hydroxyimino-3,4-dihydro-2H-chromen-7-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-1100)

(140a) benzyl 4-(4-acetyl-3-hydroxyphenyl)-1,4- diazepane-1-carboxylate

The reaction was performed following a method described in Example 59 (59a) using 4'-fluoro-2'-hydroxyacetophenone and benzyl 1-homopiperazinecarboxylate and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 2948, 1699, 1631, 1521, 1424, 1370, 1331, 1232, 928, 754 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.93-2.02 (2H, m), 2.49 (3H, s), 3.33 (1H, t, J = 6.3 Hz), 3.40 (1H, t, J = 5.9 Hz), 3.56-3.64 (6H, m), 5.10 (1H, s), 5.14 (1H, s), 6.11-6.12 (1H, m), 6.20-6.23 (1H, m), 7.30-7.36 (5H, m), 7.52 (0.5H, d, J = 8.8 Hz), 7.54 (0.5H, d, J = 8.8 Hz), 12.85 (0.5H, s), 12.86 (0.5H, s);

MS (FAB) m/z: 369 $[M+H]^+$, 353, 327, 273, 242, 226, 165, 65.

(140b) benzyl 4-{4-[(2E)-3-(dimethylamino)prop-2-enoyl]-3-hydroxyphenyl}-1,4-diazepane-1-carboxylate

An N,N-dimethylformamide dimethylacetal (13 mL, 99 mmol) solution of benzyl 4-(4-acetyl-3-hydroxyphenyl)-1,4- diazepane-1-carboxylate (3.64 g, 9.9 mmol) which was produced in Example 140 (140a) was stirred at 100°C for two hours. Ethyl acetate (100 mL) was added to the reaction liquid, and the organic layer was washed with water (100 mL) twice, and the solvent was evaporated under reduced pressure after drying over sodium sulfate. The obtained residue was purified by silica gel column chromatography (100% ethyl acetate) and the title compound was obtained (3.67 g, yield 88%).

Yellow foam

IR (KBr) $\nu_{max}$ 2936, 1698, 1622, 1545, 1361, 1241, 1115 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.95-2.03 (2H, m), 2.84-3.12 (6H, m), 3.31 (1H, t, J = 6.4 Hz), 3.38 (1H, t, J = 5.9 Hz), 3.54-3.64 (6H, m), 5.10 (1H, s), 5.14 (1H, s), 5.65 (1H, d, J = 12.2 Hz), 6.14-6.17 (2H, m), 7.30-7.36 (5H, m), 7.53-7.55 (1H, m), 7.79 (1H, d, J = 12.2 Hz);

MS (FAB) m/z: 424 $[M+H]^+$, 353, 273, 242, 226, 165, 65;

Anal. Calcd for $C_{24}H_{29}N_3O_4 \cdot 0.5H_2O$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.52; H, 6.64; N, 9.46.

(140c) benzyl 4-(4-oxo-4H-chromen-7-yl)-1,4-diazepane-1-carboxylate

80% acetic acid aqueous solution (10 mL) of benzyl 4-{4-[(2E)-3-(dimethylamino)prop-2-enoyl]-3-hydroxyphenyl}-1,4-diazepane-1-carboxylate (3.67 g, 8.7 mmol) which was produced in Example 140 (140b) was stirred at 100°C for two hours. Ethyl acetate (100 mL) was added to the reaction liquid and the organic layer was washed with water (100 mL) and a sodium hydrogen carbonate aqueous solution (100 mL), and the solvent was evaporated under reduced pressure after drying over sodium sulfate. The obtained residue was purified by silica gel column chromatography (ethyl acetate/methanol =20:1) and the title compound was obtained (3.19 g, yield 97%).

Yellow liquid

IR (film) $\nu_{max}$ 2951, 1697, 1626, 1588, 1446, 1411, 1230, 928, 754 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.95-2.04 (2H, m), 3.55 (1H, t, J = 6.3 Hz), 3.43 (1H, t, J = 6.4 Hz), 3.61-3.69 (6H, m), 5.07 (1H, s), 5.13 (1H, s), 6.20 (1H, d, J = 6.4 Hz), 6.48-6.50 (1H, m), 6.73-6.77 (1H, m), 7.28-7.33(5H, m), 7.68(1H, d, J = 6.4 Hz), 8.00-8.03 (1H, m);

MS (FAB) m/z: 379 $[M+H]^+$, 353, 273, 243, 226, 165, 91, 65;

Anal. Calcd for $C_{22}H_{22}N_2O_4 \cdot 0.5H_2O$: C, 68.20; H, 5.98; N, 7.23. Found: C, 68.41; H, 5.89; N, 7.15.

(140d) 7-(1,4-diazepan-1-yl)-2,3-dihydro-4H-chromen-4-one

benzyl 4-(4-oxo-4H-chromen-7-yl)-1,4-diazepane-1-carboxylate (1.98 g, 5.2 mmol) which was produced in Example 140 (140c) was subjected to hydrogenolysis in ethanol (50 mL) solvent under normal pressure hydrogen atmosphere in the presence of 10% palladium-carbon catalyst (2.23 g, 1.0 mmol) for six hours. The

catalyst was removed from the reaction liquid and the title compound was obtained (1.07 g, yield 84%) by evaporating the solvent under reduced pressure.

Orange liquid

IR (film) $\nu_{max}$ 3322, 2934, 1663, 1601, 1406, 1143, 824 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.89 (2H, quint, J = 5.9 Hz), 2.70 (2H, t, J = 6.4 Hz), 2.83 (2H, t, J = 5.4 Hz), 3.02 (2H, t, J = 5.4 Hz), 3.57 (2H, t, J = 5.4 Hz), 3.62 (2H, t, J = 5.9 Hz), 4.47 (2H, t, J = 6.8 Hz), 6.10 (1H, d, J = 2.4 Hz), 6.39 (1H, dd, J = 2.4, 8.8 Hz), 7.77 (1H, d, J = 8.8 Hz);

MS (EI) m/z: 246 [$M^+$], 204, 190, 178, 176, 162, 123, 119, 69, 56, 44, 43.

(140e) 4-[4-(4-oxo-3,4-dihydro-2H-chromen-7-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) using 7-(1,4-diazepan-1-yl)-2,3-dihydro-4H-chromen-4-one which was produced in Example 140 (140d) and the title compound was synthesized.

Brown solid

Mp 190-201°C(dec.);

IR (KBr) $\nu_{max}$ 2957, 2207, 1602, 1516, 1405, 1253, 1141, 926 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.88-1.93 (2H, m), 2.59 (2H, t, J = 5.9 Hz), 3.60 (2H, t, J = 5.5 Hz), 3.75 (2H, t, J = 5.9 Hz), 3.81 (2H, t, J = 5.1 Hz), 3.92-3.95 (2H, m), 4.41 (2H, t, J = 5.9 Hz), 6.24 (1H, d, J = 2.4 Hz), 6.43 (1H, d, J = 7.4 Hz), 6.53 (1H, dd, J = 2.0, 9.0 Hz), 7.36 (1H, d, J = 7.4 Hz), 7.53 (1H, d, J = 9.0 Hz), 12.55 (1H, brs);

MS (FAB) m/z: 381 $[M+H]^+$, 273, 258, 242, 226, 216, 165, 63, 52.

(140f) 4-[4-(4-hydroxyimino-3,4-dihydro-2H-chromen-7-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 120 using 4-[4-(4-oxo-3,4-dihydro-2H-chromen-7-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 140 (140e) and the title compound was synthesized.

Brown solid

Mp >290°C;

IR (KBr) $\nu_{max}$ 2948, 2210, 1625, 1552, 1520, 1256, 1144, 1063, 776 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.90-1.93 (2H, m), 2.74 (2H, t, J = 5.9 Hz), 3.53 (2H, t, J = 5.9 Hz), 3.74 (4H, brs), 3.92-3.94 (2H, m), 4.41 (2H, t, J = 5.9 Hz), 6.21 (1H, d, J = 2.4 Hz), 6.44 (1H, d, J = 7.8 Hz), 6.47 (1H, dd, J = 2.4, 8.8 Hz), 7.38 (1H, d, J = 7.8 Hz), 7.56 (1H, d, J = 8.8 Hz), 10.68 (1H, s);

MS (FAB) m/z: 396 $[M+H]^+$, 378, 273, 242, 226, 65.

(140 g) 3-amino-4-[4-(4-hydroxyimino-3,4-dihydro-2H-chromen-7-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-[4-(4-hydroxyimino-3,4-dihydro-2H-chromen-7-yl)-1,4-diazepan-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 140 (140f) and the title compound was synthesized.

White powder

Mp 178-183°C (dec.);

IR (KBr) $\nu_{max}$ 3441, 3327, 1606, 1513, 1369, 1183, 1061, 919, 828 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 2.11-2.15 (2H, m), 2.75 (2H, t, J = 6.3 Hz), 3.17 (2H, brs), 3.26 (2H, brs), 3.53-3.56 (2H, m), 3.75-3.77 (2H, m), 4.11 (2H, t, J = 6.3 Hz), 6.19 (1H, d, J = 2.7 Hz), 6.45 (1H, dd, J = 2.7, 9.0 Hz), 6.97 (2H, brs), 7.07 (1H, d, J = 5.4 Hz), 7.08 (2H, brs), 7.56 (1H, d, J = 9.0 Hz), 8.38 (1H, d, J = 5.4 Hz), 10.63 (1H, s);

HRMS m/z calcd for $C_{22}H_{25}O_3N_6S$ 453.1709, found 453.1718;

MS (FAB) m/z: 453 $[M+H]^+$, 452, 435, 418, 273, 242, 176, 65.

(Example 141) 3-amino-6-methyl-4-(4-phenyl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-161)

(141a) [1-(4-phenyl-1,4-diazepan-1-yl)ethylidene]malononitrile

The reaction was performed following a method described in Example 75 (75b) using 1-phenyl homopiperazine in place of 1-phenylpiperazine and the title compound was obtained.

White powder

Mp 113-114°C;

IR (KBr) $\nu_{max}$ 2957, 2204, 1598, 1562, 1504, 1464, 1356, 928, 754 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.94 (2H, brs), 2.22 (3H, brs), 3.57 (2H, t, J = 5.5 Hz), 3.61-4.02 (6H, m), 6.62 (1H, t, J = 7.0 Hz), 6.78 (2H, d, J = 8.2 Hz), 7.16 (2H, dd, J = 7.0, 9.0 Hz);

HRMS m/z calcd for $C_{16}H_{18}N_4$ 266.1533, found 266.1525;

MS (EI) m/z: 266 $[M^+]$, 265, 237, 210, 201, 184, 160, 146, 132, 120, 106, 91, 77, 42, 41;

Anal. Calcd for $C_{16}H_{18}N_4 \cdot 0.1H_2O$: C, 71.67; H, 6.84; N, 20.89. Found: C, 71.55; H, 6.76; N, 21.00.

(141b)[(2E)-3-(dimethylamino)-1-(4-phenyl-1,4-diazepan-1-yl)but-2-enylidene]malononitrile

The reaction was performed following a method described in Example 75 (75c) using [1-(4-phenyl-1,4-diazepan-1-yl)ethylidene]malononitrile which was produced in Example 141 (141a) and the title compound was obtained.

Pale brown powder

Mp 236-238°C (dec.);

IR (film) $\nu_{max}$ 2933, 2195, 1722, 1645, 1505, 1440, 1026, 752 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 2.01-2.07 (2H, m), 2.19 (3H, s), 2.97 (6H, s), 3.57 (2H, t, J = 5.9 Hz), 3.63 (2H, t, J = 5.9 Hz), 3.71 (2H, t, J = 5.1 Hz), 3.83 (2H, t, J = 5.9 Hz), 4.30 (1H, s), 6.70-6.73 (3H, m), 7.22 (2H, d, J = 8.6 Hz);

HRMS m/z calcd for $C_{20}H_{25}N_5$ 335.2109, found 335.2122;

MS (EI) m/z: 335 [$M^+$], 320, 292, 291, 229, 203, 168, 159, 120, 91, 85, 72, 56;

Anal. Calcd for $C_{20}H_{25}N_5$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.85; H, 7.56; N, 20.57.

(141c) 6-methyl-2-oxo-4-(4-phenyl-1,4-diazepan-1-yl)-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 75 (75d) using [(2E)-3-(dimethylamino)-1-(4-phenyl-1,4-diazepan-1-yl)but-2-enylidene]malononitrile which was produced in Example 141 (141b) and the title compound was obtained.

White powder

Mp 132-133°C;

IR (KBr) $\nu_{max}$ 2957, 2199, 1625, 1503, 1459, 1351, 1216, 931, 751, 692 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 1.91-1.95 (2H, m), 2.08 (3H, s), 3.51 (2H, t, J = 6.3 Hz), 3.65-3.70 (4H, m), 3.91 (2H, t, J = 5.4 Hz), 5.88 (1H, s), 6.60 (1H, t, J = 7.3 Hz), 6.78 (2H, d, J = 7.3 Hz), 7.16 (2H, t, J = 7.3 Hz), 11.20 (1H, brs);

HRMS m/z calcd for $C_{18}H_{21}ON_4$ 309.1715, found 309.1713;

MS (FAB) m/z: 309, 273, 258, 246, 226, 216, 202, 189, 176, 165, 120, 65.

(141d) 2-chloro-6-methyl-4-(4-phenyl-1,4-diazepan-1-yl)nicotinonitrile

The reaction was performed following a method described in Example 75 (75e) using 6-methyl-2-oxo-4-(4-phenyl-1,4-diazepan-1-yl)-1,2-dihydropyridine-3-carbonitrile which was produced in Example 141 (141c) and the title compound was obtained.

White powder

Mp 132-133°C;

IR (KBr) $\nu_{max}$ 3438, 2211, 1593, 1504, 1355, 1220, 1040, 929, 750 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 2.14 (2H, quint, J = 5.9 Hz), 2.41 (3H, s), 3.57 (2H, t, J = 6.3 Hz), 3.71 (2H, t, J = 5.9 Hz), 3.78 (2H, t, J = 4.9 Hz), 3.98 (2H, t, J = 3.9 Hz), 6.42 (1H, s), 6.72-6.75 (3H, m), 7.24 (2H, d, J = 7.3 Hz);

HRMS m/z calcd for $C_{18}H_{20}N_4Cl$ 327.1377, found 327.1371;

MS (FAB) m/z: 327 $[M+H]^+$, 326, 273, 242, 226, 165, 120, 65.

(141e) 6-methyl-4-(4-phenyl-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

An ethanol (200 mL) suspension of 2-chloro-6-methyl-4-(4-phenyl-1,4-diazepan-1-yl)nicotinonitrile (6.67 g, 20.4 mmol) which was produced in Example 141 (141d) and thiourea (7.77 g, 102.1 mmol) was heated under reflux for three hours. The reaction liquid was cooled to room temperature and the generated crystal was filtered and the title compound was obtained (5.91 g, yield 89%).

White powder

Mp 250-253°C;

IR (KBr) $\nu_{max}$ 2962, 2204, 1628, 1598, 1547, 1504, 1351, 1207, 926, 750 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.93-1.98 (2H, m), 2.19 (3H, s), 3.53 (2H, t, J = 5.5 Hz), 3.70-3.74 (4H, m), 3.94 (2H, t, J = 5.9 Hz), 6.33 (1H, s), 6.60 (1H, t, J = 8.2 Hz), 6.78 (2H, d, J = 8.2 Hz), 7.16 (2H, t, J = 8.2 Hz), 12.49 (1H, brs);

HRMS m/z calcd for $C_{18}H_{22}N_4S$ 325.1487, found 325.1501;

MS (FAB) m/z: 325 $[M+H]^+$, 324, 273, 192, 178, 165, 65, 51, 39.

(141f) 3-amino-6-methyl-4-(4-phenyl-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 6-methyl-4-(4-phenyl-1,4-diazepan-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 141 (141e) and the title compound was synthesized.

Pale yellow powder

Mp 283-286°C;

IR (KBr) $\nu_{max}$ 3441, 3323, 1645, 1596, 1504, 1367, 1203, 749, 692 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 2.12-2.14 (2H, m), 2.45 (3H, s), 3.17 (2H, brs), 3.27-3.31 (2H, m), 3.55 (2H, t, J = 6.4 Hz), 3.77 (2H, t, J = 4.4 Hz), 6.61 (1H, t, J = 7.3 Hz), 6.77 (2H, d, J = 7.3 Hz), 6.95 (1H, s), 6.96 (2H, brs), 7.00 (2H, brs), 7.17 (2H, t, J = 7.3 Hz);

HRMS m/z calcd for $C_{20}H_{24}ON_5S$ 382.1701, found 382.1696;

MS (EI) m/z: 382 $[M+H]^+$, 365, 363, 325, 323, 244, 232, 218, 158, 146, 120, 106, 77, 75, 57, 45;

Anal. Calcd for $C_{20}H_{23}N_5OS \cdot 0.5H_2O$: C, 61.51; H, 6.19; N, 17.93; S, 8.21. Found: C, 61.35; H, 5.85; N, 17.92; S, 8.14.

(Example 142) 3-amino-4-(4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepan-1-yl)-6-methylthieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 3-182)

(142a) 4-[4-(2,2-dicyano-1-methylvinyl)-1,4-diazepan-1-yl]-N,N-dimethylbenzamide

The reaction was performed following a method described in Example 75 (75b) using 4-(1,4-diazepan-1-yl)-N,N-dimethylbenzamide which was produced in Example 128 (128d) in place of 1-phenylpiperazine and the title compound was obtained.

Colourless liquid

IR (film) $\nu_{max}$ 3439, 2935, 2206, 1608, 1562, 1493, 1396, 1190 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 2.11 (2H, brs), 2.31 (3H, s), 3.07 (6H, s), 3.55-3.97 (8H, m), 6.68 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz);

MS (EI) m/z: 337 [$M^+$], 293, 266, 265, 203, 174, 160, 146, 132, 118, 104, 77, 72, 40.

(142b) 4-{4-[(2E)-1-(dicyanomethylene)-3-(dimethylamino)but-2-en-1-yl]-1,4-diazepan-1-yl}-N,N-dimethylbenzamide

The reaction was performed following a method described in Example 75 (75c) using 4-[4-(2,2-dicyano-1-methylvinyl)-1,4-diazepan-1-yl]-N,N-dimethylbenzamide which was produced in Example 142 (142a) and the title compound was obtained.

Yellow foam

IR (film) $\nu_{max}$ 2926, 2194, 1607, 1561, 1493, 1440, 1390, 1187, 1025, 763, 554 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 2.03-2.06 (2H, m), 2.20 (3H, s), 2.99 (6H, s), 3.07 (6H, s), 3.60-3.63 (4H, m), 3.75-3.78 (2H, m), 3.83-3.84 (2H, m), 4.31 (1H, s), 6.69 (2H, d, J = 8.8 Hz), 7.38 (2H, d, J = 8.8 Hz);

MS (FAB) m/z: 407 $[M+H]^+$, 406, 362, 273, 242, 203, 165, 39, 31.

(142c) 4-[4-(3-cyano-6-methyl-2-oxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]-N,N-dimethylbenzamide

The reaction was performed following a method described in Example 75 (75d) using 4-{4-[(2E)-1-(dicyanomethylene)-3-(dimethylamino)but-2-en-1-yl]-1,4-

diazepan-1-yl}-N,N-dimethylbenzamide which was produced in Example 142 (142b) and the title compound was obtained.

Brown powder

Mp 220-223°C;

IR (KBr) $\nu_{max}$ 3434, 2939, 2199, 1621, 1526, 1494, 1454, 1391, 1355, 1189 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) $\delta$ 1.90-1.96 (2H, m), 2.08 (3H, s), 2.95 (6H, s), 3.55-3.57 (2H, m), 3.67-3.69 (2H, m), 3.72-3.74 (2H, m), 3.91-3.93 (2H, m), 5.89 (1H, s), 6.68 (2H, d, J = 8.8 Hz), 7.27 (2H, d, J = 8.8 Hz), 11.20 (1H, brs);

MS (FAB) m/z: 380 $[M+H]^+$, 349, 335, 273, 258, 242, 93, 65.

(142d) 4-[4-(2-chloro-3-cyano-6-methylpyridin-4-yl)-1,4-diazepan-1-yl]-N,N-dimethylbenzamide

The reaction was performed following a method described in Example 75 (75e) using 4-[4-(3-cyano-6-methyl-2-oxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]-N,N-dimethylbenzamide which was produced in Example 142 (142c) and the title compound was obtained.

White powder

Mp 199-201°C;

IR (KBr) $\nu_{max}$ 2946, 2210, 1618, 1590, 1515, 1392, 1219, 1189, 1038, 926, 830, 763 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 2.14 (2H, quint, J = 5.9 Hz), 2.42 (3H, s), 3.07 (6H, s), 3.60 (2H, t, J = 5.9 Hz), 3.69 (2H, t, J = 5.9 Hz), 3.82 (2H, t, J = 4.9 Hz), 3.98 (2H, t, J = 4.9 Hz), 6.43 (1H, s), 6.70 (2H, d, J = 8.8 Hz), 7.38 (2H, d, J = 8.8 Hz);

MS (FAB) m/z: 398 $[M+H]^+$, 397, 353, 246, 242, 182.

(142e) 4-[4-(3-cyano-6-methyl-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]-N,N-dimethylbenzamide

The reaction was performed following a method described in Example 141 (141e) using 4-[4-(2-chloro-3-cyano-6-methylpyridin-4-yl)-1,4-diazepan-1-yl]-N,N-dimethylbenzamide which was produced in Example 142 (142d) and the title compound was obtained.

White powder

Mp 175-178°C;

IR (KBr) $\nu_{max}$ 3205, 2969, 2201, 1607, 1551, 1485, 1352, 1185, 929 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.92-1.97 (2H, m), 2.19 (3H, s), 2.95 (6H, s), 3.56-5.58 (2H, m), 3.72-3.77 (4H, m), 3.95-3.96 (2H, m), 6.34 (1H, s), 6.79 (2H, d, J = 8.6 Hz), 7.27 (2H, d, J = 8.6 Hz), 12.51 (1H, brs);

MS (FAB) m/z: 396 $[M+H]^+$, 367, 351, 335, 273, 246, 242, 165.

(142f) 3-amino-4-(4-{4-[(dimethylamino)carbonyl)phenyl}-1,4-diazepan-1-yl)-6-methylthieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-[4-(3-cyano-6-methyl-2-thioxo-1,2-dihydropyridin-4-yl)-1,4-diazepan-1-yl]-N,N-dimethylbenzamide which was produced in Example 142 (142e) and the title compound was synthesized.

White powder

Mp 158-162°C;

IR (KBr) $\nu_{max}$ 3436, 3322, 3182, 1607, 1492, 1371, 1189 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 500 MHz) δ 2.14-2.16 (2H, m), 2.45 (3H, s), 2.97 (6H, s), 3.16 (2H, brs), 3.28 (2H, brs), 3.59 (2H, t, J = 5.9 Hz), 3.82 (2H, t, J = 4.9 Hz), 6.78 (2H, d, J = 8.8 Hz), 6.96 (1H, s), 6.96 (2H, brs), 7.02 (2H, brs), 7.30 (2H, d, J = 8.8 Hz);

HRMS m/z calcd for $C_{23}H_{29}O_2N_6S$ 453.2027, found 453.2044;

MS (ESI) m/z: 453 $[M+H]^+$, 440;

Anal. Calcd for $C_{23}H_{28}N_6O_2S \cdot 4.32H_2O$: C, 52.08; H, 6.96; N, 15.84; S, 6.05. Found: C, 51.75; H, 6.72; N, 15.84; S, 5.91.

(Example 143) 3-amino-4-(3-methoxypiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-28)

(143a) 4-(3-methoxypiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 118 (118c) using 3-methoxy piperidine (J. Med.Chem. 8,766, (1965)) and the title compound was obtained.

Brown powder

Mp 148-152°C;

IR (KBr) $\nu_{max}$ 2943, 2207, 1622, 1515, 1303, 1250, 1167, 1097, 985, 778 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 1.47-1.62 (2H, m), 1.76-1.83 (1H, m), 1.87-1.93 (1H, m), 3.25 (3H, s), 3.35-3.40 (1H, m), 3.44-3.52 (2H, m), 3.58-3.63 (1H, m), 3.86 (2H, dd, J = 2.4, 13.3 Hz), 6.48 (1H, d, J = 7.4 Hz), 7.44 (1H, d, J = 7.4 Hz), 12.60 (1H, brs);

HRMS m/z calcd for $C_{12}H_{15}ON_3S$ 249.0935, found 249.0919;

MS (FAB) m/z: 250 $[M+H]^+$, 218, 180, 39.

(143b) 3-amino-4-(3-methoxypiperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-(3-methoxypiperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 143 (143a) and the title compound was obtained.

Pale yellow powder

Mp 182-185°C;

IR (KBr) $\nu_{max}$ 3412, 3321, 3146, 2936, 1660, 1585, 1502, 1373, 1246, 1099, 977 $cm^{-1}$;

$^1$H NMR(DMSO-$d_6$, 500 MHz) δ 1.49-2.09 (4H, m), 2.81-3.46 (4H, m), 3.32 (3H, s), 3.54-3.58 (1H, m), 6.99 (2H, brs), 7.05 (1H, d, J = 5.4 Hz), 7.09 (2H, brs), 8.44 (1H, d, J = 5.4 Hz);

HRMS m/z calcd for $C_{14}H_{18}O_2N_4S$ 306.1151, found 306.1154;

MS (EI) m/z: 306 [$M^+$], 274, 256, 229, 218, 202, 176, 175, 148, 147, 105, 104, 58, 41;

Anal. Calcd for $C_{14}H_{18}N_4O_2S$: C, 54.88; H, 5.92; N, 18.29; S, 10.47. Found: C, 54.81; H, 5.71; N, 18.11, 10.47.

(Example 144) 3-amino-4-[3-(ethoxymethyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-22)

(144a) tert-butyl 3-(ethoxymethyl)piperidine-1-carboxylate

The reaction was performed following a method described in Example 101 (101a) using ethyl iodide in place of methyl iodide and the title compound was obtained as an oil. Yield 82%.

IR (neat) $\nu_{max}$ 1697, 1423, 1152 $cm^{-1}$;

$^1$H NMR ($CDCl_3$, 400MHz) δ 1.16-1.27 (1H, m), 1.19 (3H, t, J = 7.0 Hz), 1.38-1.50 (1H, m), 1.46 (9H, s), 1.60-1.66 (1H, m), 1.72-1.83 (2H, m), 2.48-2.91 (2H, m), 3.28 (2H, d, J = 6.3 Hz), 3.41-3.51 (2H, m), 3.80-4.15 (2H, m);

MS (EI) m/z: 243 [$M^+$], 114, 57, 41.

(144b) 3-(ethoxymethyl)piperidine

4N hydrochloric acid-1,4-dioxane solution (8 mL) was added to a methanol (4 mL) solution of tert-butyl 3-(ethoxymethyl)piperidine-1-carboxylate (2.00 g, 8.2 mmol) which was produced in Example 144 (144a). The reaction solution was concentrated under reduced pressure after being stirred at room temperature for two hours. The obtained residue was treated with 1N aqueous solution of sodium

hydroxide (20 mL) and the aqueous layer was extracted with methylene chloride (3x30 mL). The extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure and 1.01 g of the title compound was obtained (yield 86%) as an oil.

IR (neat) $\nu_{max}$ 3310, 1625, 1553, 1270, 1113 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.04-1.15 (1H, m), 1.18 (3H, t, J = 7.0 Hz), 1.39-1.50 (1H, m), 1.60 (1H, br), 1.59-1.83 (3H, m), 2.32 (1H, dd, J = 10.2, 12.1 Hz), 2.55 (1H, dt, J = 3.1, 11.7 Hz), 2.99 (1H, brd, J = 12.1 Hz), 3.12 (1H, brd, J = 11.7 Hz), 3.23 (2H, d, J = 6.3 Hz), 3.39-3.50 (2H, m);

MS (EI) m/z: 143 [$M^+$], 114, 44.

(144c) (2Z)-2-cyano-3-[3-(ethoxymethyl)piperidin-1-yl]but-2-enethioamide

The reaction was performed following a method described in Example 5 (5a) using 3-(ethoxymethyl)piperidine which was produced in Example 144 (144b) in place of isobutylamine and the title compound was obtained. Yield 86%.

Mp 146-148°C;

IR (KBr) $\nu_{max}$ 3335, 3277, 3142, 2189, 1627, 1542, 1396, 1110 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.10 (3H, t, J = 7.0 Hz), 1.26-1.93 (5H, m), 2.27 (3H, s), 2.93 (1H, dd, J = 10.2, 13.7 Hz), 3.05-3.12 (1H, m), 3.20-3.30 (2H, m), 3.34-3.46 (2H, m), 3.51-3.62 (2H, m), 8.19 (1H, br), 8.93 (1H, br);

MS (EI) m/z: 267 [$M^+$], 234, 204;

Anal. Calcd for $C_{13}H_{21}N_3SO$: C, 58.39; H, 7.92; N, 15.71; S, 11.99. Found: C, 58.40; H, 7.99; N, 15.60; S, 12.06.

(144d) 4-[3-(ethoxymethyl)piperidin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 5 (5b) using (2Z)-2-cyano-3-[3-(ethoxymethyl)piperidin-1-yl]but-2-enethioamide which was produced in Example 144 (144c) and a crude crystal of the title compound was obtained.

Mp 151-154°C;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.10 (3H, t, J = 7.0 Hz), 1.26-1.90 (5H, m), 3.08 (1H, dd, J = 10.2, 13.3 Hz), 3.19-3.45 (5H, m), 3.91-3.99 (2H, m), 6.45 (1H, d, J = 7.4 Hz), 7.42-7.45 (1H, m), 12.59 (1H, br).

(144e) 3-amino-4-[3-(methoxymethyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using a crude crystal of 4-[3-(ethoxymethyl)piperidin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 144 (144d) and the title compound was obtained. Yield 34% from (2Z)-2-cyano-3-[3-(ethoxymethyl)piperidin-1-yl]but-2-enethioamide.

Mp 125-126°C;

IR (KBr) $\nu_{max}$ 3439, 3323, 3174, 1650, 1580, 1501, 1372, 1106 cm$^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.01-1.17 (1H, m), 1.08 (3H, t, J = 7.0 Hz), 1.73-1.85 (3H, m), 2.05-2.16 (1H, m), 2.34-2.70 (2H, m), 3.21-3.46 (6H, m), 6.92 (2H, br), 7.00 (1H, d, J = 5.5 Hz), 7.09 (2H, br), 8.41 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 335 $[M + H]^+$;

Anal. Calcd for $C_{16}H_{22}N_4SO_2 \cdot 0.6\ H_2O$: C, 55.66; H, 6.77; N, 16.23; S, 9.29. Found: C, 55.44; H, 6.63; N, 16.33; S, 9.41.

(Example 145) 3-amino-4-{3-[(2-methoxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-112)

(145a) tert-butyl 3-[(2-methoxyethoxy)methyl]piperidine-1-carboxylate

A toluene (2 mL) solution of 3-(hydroxymethyl)piperidine-1-carboxylate (Bioorg. Med. Chem. Lett. 8, (1998), 1595-1600) (215 mg, 1 mmol) and 1-bromo-2-methoxyethane (278 mg, 0.19 mL, 2 mmol) was blended with tetra-n-butylammonium bisulfate (68 mg, 0.2 mmol) and 50% aqueous solution of sodium hydroxide (1 mL) and the resultant mixture was stirred at room temperature for 20 hours. The reaction mixture was partitioned with water (30 mL) and ethyl acetate (50 mL) and the organic layer was dried over sodium sulfate after being washed with a saturated saline solution (30 mL), and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel chromatography (hexane/ethyl acetate, 2:1) and 177 mg of the title compound was obtained (65%) as an oil.

IR (neat) $\nu_{max}$ 1695, 1423, 1152 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 1.14-1.24 (1H, m), 1.38-1.49 (1H, m), 1.45 (9H, s), 1.59-1.66 (1H, m), 1.76-1.85 (2H, m), 2.52-2.85 (2H, m), 3.32 (2H, d, J = 5.9 Hz), 3.38 (3H, s), 3.50-3.58 (4H, m), 3.82-4.04 (2H, m);

MS (EI) m/z: 273 [$M^+$], 172, 114, 57;

Anal. Calcd for $C_{14}H_{27}NO_4 \cdot 0.1\ H_2O$: C, 61.11; H, 9.96; N, 5.09. Found: C, 61.01; H, 9.57; N, 5.13.

(145b)3-[(2-methoxyethoxy)methyl]piperidine

A methanol (2 mL) solution of tert-butyl 3-[(2-methoxyethoxy)methyl]piperidine-1-carboxylate (0.87 g, 3.2 mmol) which was produced in Example 145 (145a) was blended with 4N hydrochloric acid-1,4-dioxane solution (3 mL) and the resultant solution was stirred at room temperature for two hours. 1N aqueous solution of sodium hydroxide (10 mL) was added to the residue which was obtained by concentrating the reaction mixture under reduced pressure

and the aqueous layer was extracted with methylene chloride (3x30 mL). After the extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure and 0.51 g of the title compound was obtained (92%) as an oil.

IR (neat) $\nu_{max}$ 3413, 1626, 1271, 1111 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 1.05-1.15 (1H, m), 1.40-1.51 (1H, m), 1.62-1.86 (3H, m), 1.76 (1H, br), 2.33 (1H, dd, J = 9.8, 12.1 Hz), 2.56 (1H, ddd, J = 2.7, 11.7, 12.1 Hz), 3.00 (1H, brd, J = 12.1 Hz), 3.14 (1H, brd, J = 11.7 Hz), 3.33 (2H, d, J = 6.3 Hz), 3.39 (3H, s), 3.48-3.60 (4H, m);

MS (EI) m/z: 173 [$M^+$], 114, 44;

Anal. Calcd for $C_9H_{19}NO_2 \cdot 0.2\ H_2O$: C, 61.12; H, 11.06; N, 7.92. Found: C, 61.15; H, 10.67; N, 7.86.

(145c) 3-amino-4-{3-[(2-methoxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

3-[(2-methoxyethoxy)methyl]piperidine (0.50 g, 2.9 mmol) which was produced in Example 145 (145b) and (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J.Org.Chem. (1962), 27,2433-2439) (0.41 g, 2.4 mmol) were mixed with ethanol (3 mL) and the resultant mixture was stirred at room temperature for one hour. The residue obtained by concentrating the reaction mixture under reduced pressure was dissolved in toluene (8 mL) and was blended with N,N-dimethylformamide dimethylacetal (0.86 g, 0.96 mL, 7.2 mmol) and the resultant mixture was stirred under reflux for 30 minutes. After the solvent was evaporated under reduced pressure, 1N aqueous solution of sodium hydroxide (8 mL) was added to the residue and the mixture was stirred and heated under reflux for one hour. After cooling, the reaction mixture was partitioned with water and ether. The obtained aqueous layer was neutralized with 1N hydrochloric acid (8 mL) and extracted with ethyl acetate (2x50 mL). The solvent was evaporated under reduced pressure after the extract

was dried over sodium sulfate. The residue was dissolved in N,N-dimethylformamide (5 mL) and the resultant solution was blended with 2-chloroacetamide (0.15 g, 1.6 mmol) and 8N aqueous solution of sodium hydroxide (0.5 mL) and the mixture was stirred at room temperature for one hour. The reaction mixture was blended with water (50 mL) and extracted with ethyl acetate (2x50 mL). After the extract was dried over sodium sulfate, the residue which was obtained by evaporating the solvent under reduced pressure was purified by silica gel column chromatography (100% ethyl acetate) and 0.25 g of the title compound was obtained (yield 28%).

Mp 138-139°C;

IR (KBr) $\nu_{max}$ 3433, 3323, 3178, 1651, 1579, 1501, 1372, 1088 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) δ 1.00-1.15 (1H, m), 1.73-1.83 (3H, m), 2.07-2.16 (1H, m), 2.31-2.70 (2H, m), 3.21 (3H, s), 3.25-3.53 (8H, m), 6.92 (2H, br), 7.00 (1H, d, J = 5.5 Hz), 7.09 (2H, br), 8.41 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 365 $[M + H]^+$.

(Example 146) 3-amino-4-{3-[(2-ethoxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-123)

(146a) tert-butyl 3-[(2-ethoxyethoxy)methyl]piperidine-1-carboxylate

The reaction was performed following a method described in Example 101 (101a) using 2-bromoethyl ethyl ether in place of methyl iodide and the title compound was obtained as an oil. Yield 56%.

IR (neat) $\nu_{max}$ 1696, 1423, 1152 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.14-1.25 (1H, m), 1.21 (3H, t, J = 7.0 Hz), 1.37-1.51 (1H, m), 1.45 (9H, s), 1.60-1.67 (1H, m), 1.75-1.86 (2H, m), 2.50-2.86 (2H, m), 3.30-3.37 (2H, m), 3.54 (2H, q, J = 7.0 Hz), 3.50-3.67 (4H, m), 3.84-4.08 (2H, m);

MS (FAB) m/z: 288 $[M + H]^+$.

(146b) 3-[(2-methoxyethoxy)methyl]piperidine

The reaction was performed following a method described in Example 144 (144b) using tert-butyl 3-[(2-ethoxyethoxy)methyl]piperidine-1-carboxylate which was produced in Example 146 (146a) and the title compound was obtained as an oil. Yield 92%.

IR (neat) $\nu_{max}$ 3410, 1640, 1273, 1114 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 1.05-1.15 (1H, m), 1.21 (3H, t, J = 7.0 Hz), 1.40-1.51 (1H, m), 1.62-1.85 (3H, m), 1.75 (1H, br), 2.33 (1H, dd, J = 10.0, 12.0 Hz), 2.56 (1H, dt, J = 3.0, 12.0 Hz), 3.01 (1H, brd, J = 12.0 Hz), 3.15 (1H, brd, J = 12.0 Hz), 3.27-3.83 (2H, m), 3.54 (2H, q, J = 7.0 Hz), 3.51-3.62 (4H, m);

MS (EI) m/z: 187 [$M^+$], 114, 44.

(146c) 4-{3-[(2-ethoxyethoxy)methyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

3-[(2-ethoxyethoxy)methyl]piperidine (0.48 g, 2.6 mmol) which was produced in Example 146 (146b) and (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J. Org. Chem. (1962), 27,2433-2439) (0.40 g, 2.3 mmol) were mixed with ethanol (5 mL) and the resultant mixture was stirred at room temperature for two hours. The residue obtained by concentrating the reaction mixture under reduced pressure was dissolved in toluene (5 mL) and the mixture was blended with N,N-dimethylformamide dimethylacetal (0.82 g, 0.92 mL, 6.9 mmol) and the mixture was stirred under reflux for 30 minutes. After the solvent was evaporated under reduced pressure, 1N aqueous solution of sodium hydroxide (5 mL) was added to the residue and the mixture was stirred under heat reflux for one hour. After cooling the mixture, the reaction mixture was partitioned with water (10 mL) and ether (50 mL). The obtained aqueous layer was neutralized with 1N hydrochloric acid (5 mL) and

extracted with ethyl acetate (2x50 mL). After the extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol =30:1) and 0.10 g of the title compound was obtained (yield 13%).

Mp 119-123°C;

IR (KBr) $\nu_{max}$ 2213, 1625, 1552, 1525, 1250, 1120, 1111 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.09 (3H, t, J = 7.0 Hz), 1.26-1.94 (5H, m), 3.09 (1H, dd, J = 9.8, 13.3 Hz), 3.20-3.52 (9H, m), 3.92-4.00 (2H, m), 6.47 (1H, d, J = 7.4 Hz), 7.43-7.47 (1H, m), 12.63 (1H, br);

MS (FAB) m/z: 322 $[M + H]^+$;

Anal. Calcd for $C_{16}H_{23}N_3SO_2$: C, 59.78; H, 7.21; N, 13.07; S, 9.98. Found: C, 59.72; H, 7.10; N, 13.09; S, 9.87.

(146d) 3-amino-4-{3-[(2-ethoxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

4-{3-[(2-ethoxyethoxy)methyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile (100 mg, 0.31 mmol) which was produced in Example 146 (146c) was dissolved in N,N-dimethylformamide (1 mL) and the resultant solution was blended with 2-chloroacetamide (38 mg, 0.40 mmol) and 8N aqueous solution of sodium hydroxide (0.1 mL) and the mixture was stirred at room temperature for one hour. Water (30 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (2x50 mL). After the extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure The obtained residue was recrystallized from ethanol (2 mL) and 62 mg of the title compound was obtained (yield 53%).

Mp 117-118°C;

IR (KBr) $\nu_{max}$ 3434, 3323, 3180, 1650, 1579, 1501, 1371, 1118 $cm^{-1}$;

$^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.00-1.15 (1H, m), 1.06 (3H, t, J = 7.0 Hz), 1.70-1.87 (3H, m), 2.06-2.19 (1H, m), 2.30-2.70 (2H, m), 3.41 (2H, q, J = 7.0 Hz), 3.25-3.54 (8H, m), 6.94 (2H, br), 7.02 (1H, d, J = 5.5 Hz), 7.10 (2H, br), 8.44 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 379 $[M + H]^+$;

Anal. Calcd for $C_{18}H_{26}N_4SO_3 \cdot 0.3\ H_2O$: C, 56.32; H, 6.98; N, 14.59; S, 8.35. Found: C, 56.16; H, 6.69; N, 14.72; S, 8.36.

(Example 147) 3-amino-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-21)

(147a) tert-butyl (3S)-3-(hydroxymethyl)piperidine-1-carboxylate

A tetrahydrofuran (50 mL) solution of di-tert-butyl dicarbonate (11.73 g, 53.7 mmol) was added dropwise to a tetrahydrofuran (100 mL) suspension of ethyl (S)-nipecotate D-tartrate (15.72 g, 51.2 mmol) and triethylamine (17.08 g, 23.5 mL, 168.8 mmol) under ice-cooling for 30 minutes. The reaction liquid was warmed to room temperature and further stirred for 15 hours. The filtrate which was obtained by removing insolubles by filtration was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed sequentially with water (50 mL), 1N hydrochloric acid (50 mL) and saturated sodium bicarbonate aqueous solution (50 mL). After the organic layer was dried over sodium sulfate, the residue which was obtained by evaporating the solvent under reduced pressure was dissolved in tetrahydrofuran (50 mL). This solution was dripped to a tetrahydrofuran (150 mL) suspension of lithium aluminum hydride (1.94 g, 51.2 mmol) under ice-cooling for 30 minutes. After the dropwise addition was completed, the reaction liquid was warmed to room temperature and further stirred at room temperature for one hour. The reaction container was transferred onto an ice bath and a little amount of ethyl acetate and saturated ammonium chloride aqueous solution were added to the

reaction liquid and the resultant liquid was stirred at room temperature further for one hour. Ethyl acetate was added to the mixture and insolubles were removed by decantation (3x100 mL). The obtained organic layer was concentrated and the residue was blended with water (100 mL) and extracted with ethyl acetate (2x100 mL). After the extract was dried over sodium sulfate, a crude crystal (10.77 g) which was obtained by evaporating the solvent under reduced pressure was recrystallized from a mixed solvent of ethyl acetate and hexane (1:5) and 9.03 g of the title compound was obtained (yield 82%).

Mp 94-97°C;

IR (KBr) $\nu_{max}$ 3489, 3466, 1674, 1434, 1154 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) $\delta$ 1.20-1.35 (1H, m), 1.35-1.50 (1H, m), 1.46 (9H, s), 1.58-1.83 (3H, m), 2.12 (1H, br), 2.75-3.24 (2H, m), 3.50 (2H, brs), 3.40-3.90 (2H, m);

MS (EI) m/z: 215 [$M^+$], 57.

Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.30; H, 9.75; N, 6.48;

$[\alpha]^{20}_D$: +18.6° (C = 1.11, EtOH).

(147b) (3S)-3-(methoxymethyl)piperidine hydrochloride

After washing in hexane (3x10 mL), sodium hydride (55% oily, 3.89 g, 89 mmol) was suspended in N,N-dimethylformamide (80 mL) and methyl iodide (14.47 g, 6.35 mL, 102 mmol) was added thereto at 0°C and subsequently a tetrahydrofuran (80 mL) solution of tert-butyl (3S)-3-(hydroxymethyl)piperidine-1-carboxylate (18.28 g, 85 mmol) which was produced in Example 147 (147a) was added dropwise for 30 minutes. The reaction mixture was warmed to room temperature and further stirred at room temperature overnight. Water (200 mL) was added to the reaction liquid and the aqueous layer was extracted with ethyl acetate (2x150 mL). The

extract was washed with a saturated saline solution (50 mL) and the solvent was evaporated under reduced pressure after drying the extract over sodium sulfate. The residue was dissolved in methanol (50 mL) and 4N hydrochloric acid-1,4-dioxane solution (50 mL) were added thereto. The reaction mixture was concentrated under reduced pressure after being stirred at room temperature for two hours. Ethyl acetate (50 mL) was added to the residue and was suspended and after the crystal was filtered, it was washed with ethyl acetate and the title compound was obtained 12.45 g (88%).

Mp 197-199°C;

IR (KBr) $\nu_{max}$ 2944, 1591, 1450, 1129, 1097, 964 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.14-1.25 (1H, m), 1.59-1.78 (3H, m), 1.97-2.08 (1H, m), 2.55-2.61 (1H, m), 2.66-2.76 (1H, m), 3.22 (3H, s), 3.14-3.26 (4H, m), 8.85-9.15 (2H, br);

MS (EI) m/z: 129 [$M^+$], 114;

$[\alpha]^{20}_D$: -12.1° (C = 1.02, MeOH).

(147c) (2Z)-2-cyano-3-[(3S)-3-(methoxymethyl)piperidin-1-yl]but-2-enethioamide

1N aqueous solution of sodium hydroxide (150 mL) was added to (3S)-3-(methoxymethyl)piperidine hydrochloride (10.76 g, 65 mmol) which was produced in Example 147 (147b) and the aqueous layer was extracted with methylene chloride (3x100 mL). The extract was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The obtained crude product of (3S)-3-(methoxymethyl)piperidine (7.56 g) was dissolved in ethanol (120 mL) and (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J.Org.Chem. (1962), 27,2433-2439) (9.47 g, 56 mmol) was added. After the reaction mixture was stirred at room temperature for 18 hours, the deposited crystal was filtered and washed with ethanol and the title compound was obtained (yield 84%).

Mp 149-151°C.

(147d) 4-[(3S)-3-(methoxymethyl)piperidin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(2Z)-2-cyano-3-[(3S)-3-(methoxymethyl)piperidin-1-yl]but-2-enethioamide (7.83 g, 31 mmol) which was produced in Example 147 (147c) and N,N-dimethylformamide dimethylacetal (4.04 g, 4.5 mL, 34 mmol) were dissolved in N,N-dimethylformamide (60 mL) and the resultant solution was stirred at room temperature for three hours and was stirred at 60°C for a further two hours. The reaction liquid was blended with a saturated saline solution (150 mL) and the aqueous layer was extracted with methylene chloride (4x100 mL). After the extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol =15:1) and 2.42 g of the title compound was obtained (yield 30%).
Mp 176-177°C.

(147e) 3-amino-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-[(3S)-3-(methoxymethyl)piperidin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 147 (147d) and the title compound was synthesized. Yield 85%.
Mp 194-196°C;
$[\alpha]^{20}_{D}$: +61.3° (C = 0.90, MeOH).

(Example 148) 3-amino-4-{(3S)-[(2-methoxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide hydrochloride (Exemplified Compound No. 1-112)

The reaction was performed following a method described in Example 145 using tert-butyl (3S)-3-(hydroxymethyl)piperidine-1-carboxylate which was produced in Example 147 (147a).

3-amino-4-{(3S)-[(2-methoxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (410 mg, 1.1 mmol) obtained was dissolved in ethanol (5 mL) and 1N hydrochloric acid (3 mL) was added. The residue which was obtained by concentrating the mixture under reduced pressure was washed with ethanol and 320 mg of the title compound (71%) was obtained as a yellow solid.

Mp 183-188°C;

IR (KBr) $\nu_{max}$ 1647, 1608, 1104 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.17-1.28 (1H, m), 1.68-1.83 (3H, m), 2.02-2.12 (1H, m), 2.78-3.05 (2H, m), 3.22 (3H, s), 3.27-3.63 (8H, m), 7.11 (1H, d, J = 5.5 Hz), 7.24 (2H, br), 8.45 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 365 $[M + H]^+$;

Anal. Calcd for $C_{17}H_{24}N_4SO_3 \cdot HCl \cdot 0.1\ H_2O$: C, 50.70; H, 6.31; N, 13.91; S, 7.96; Cl, 8.80. Found: C, 50.53; H, 6.16; N, 13.81; S, 8.08; Cl, 8.96;

$[\alpha]^{20}_D$: +82.3° (C = 1.00, MeOH).

(Example 149) 3-amino-4-{(3S)-3-[(3-methoxypropoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-115)

(149a) tert-butyl (3S)-3-[(3-methoxypropoxy)methyl]piperidine-1-carboxylate

The reaction was performed following a method described in Example 145 (145a) using tert-butyl (3S)-3-(hydroxymethyl)piperidine-1-carboxylate which was produced in Example 147 (147a) and using 1-bromo-3-methoxypropane in place of

1-bromo-2-methoxyethane and the title compound was obtained as an oil. Yield 63%.

IR (neat) $\nu_{max}$ 1696, 1423, 1152, 1119 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.13-1.25 (1H, m), 1.33-1.50 (1H, m), 1.45 (9H, s), 1.59-1.67 (1H, m), 1.72-1.85 (4H, m), 2.54-2.62 (1H, m), 2.75-2.82 (1H, m), 3.22-3.29 (2H, m), 3.32 (3H, s), 3.42-3.50 (2H, m), 3.45 (2H, t, J = 6.3 Hz), 3.86-4.02 (2H, m);

MS (FAB) m/z: 288 $[M+H]^+$, 232, 188;

Anal. Calcd for $C_{15}H_{29}NO_4$: C, 62.69; H, 10.17; N, 4.87. Found: C, 62.79; H, 9.89; N, 4.91.

(149b) (3S)-3-[(3-methoxypropoxy)methyl]piperidine

The reaction was performed following a method described in Example 144 (144b) using tert-butyl (3S)-3-[(3-methoxypropoxy)methyl]piperidine-1-carboxylate which was produced in Example 149 (149a) and the title compound was obtained as an oil. Yield 92%.

IR (neat) $\nu_{max}$ 3316, 1621, 1555, 1119 $cm^{-1}$;

$^1H$ NMR ($CDCl_3$, 400MHz) δ 1.05-1.15 (1H, m), 1.39-1.50 (1H, m), 1.62 (1H, br), 1.62-1.68 (1H, m), 1.70-1.85 (4H, m), 2.33 (1H, dd, J = 9.8, 11.7 Hz), 2.54 (1H, dt, J = 3.1, 11.7 Hz), 2.99 (1H, brd, J = 11.7 Hz), 3.11 (1H, brd, J = 11.7 Hz), 3.19-3.26 (2H, m), 3.32 (3H, s), 3.41-3.50 (4H, m);

MS (EI) m/z: 188 $[M+H]^+$, 172, 114, 99;

Anal. Calcd for $C_{10}H_{21}NO_2 \cdot 0.1\ H_2O$: C, 63.52; H, 11.30; N, 7.41. Found: C, 63.70; H, 11.23; N, 7.36.

(149c) 4-{(3S)-3-[(3-methoxypropoxy)methyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

(3S)-3-[(3-methoxypropoxy)methyl]piperidine (2.05 g, 10.7 mmol) which was produced in Example 149 (149b) and (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J.Org.Chem. (1962), 27,2433-2439) (1.77 g, 10.4 mmol) were mixed with ethanol (30 mL) and the resultant mixture was stirred at room temperature for two hours. The residue obtained by concentrating the reaction mixture under reduced pressure was dissolved in N,N-dimethylformamide (30 mL) and the resultant solution was blended with N,N-dimethylformamide dimethylacetal (1.30 g, 1.45 mL, 10.9 mmol) and the mixture was stirred at room temperature for one hour and the mixture was stirred at 60°C for a further one hour. After cooling the solution, a saturated saline solution (200 mL) was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3x100 mL). The organic layer combined was washed with a saturated saline solution (100 mL), and the solvent was evaporated under reduced pressure after drying over sodium sulfate. The residue was purified by silica gel column chromatography (ethyl acetate/methanol =15:1) and 0.54 g of the title compound was obtained (yield 16%).

Mp 137-140°C;

IR (KBr) $\nu_{max}$ 2212, 1623, 1552, 1522, 1250, 1115 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.27-1.37 (1H, m), 1.49-1.60 (1H, m), 1.69-1.93 (5H, m), 3.09 (1H, dd, J = 10.2, 12.5 Hz), 3.22 (3H, s), 3.20-3.45 (7H, m), 3.92-4.02 (2H, m), 6.47 (1H, d, J = 7.5 Hz), 7.46 (1H, d, J = 7.5 Hz), 12.62 (1H, br);

MS (EI) m/z: 321 [$M^+$], 306, 218;

Anal. Calcd for $C_{16}H_{23}N_3O_2S$: C, 59.78; H, 7.21; N, 13.07; S, 9.98. Found: C, 59.99; H, 7.15; N, 13.13; S, 9.96.

(149d) 3-amino-4-{(3S)-3-[(3-methoxypropoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-{(3S)-3-[(3-methoxypropoxy)methyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 149 (149c) and the title compound was obtained. Yield 72%.

Mp 123-124°C;

IR (KBr) $\nu_{max}$ 3421, 3324, 3154, 1656, 1580, 1372, 1111 $cm^{-1}$;

$^1H$ NMR (DMSO-$d_6$, 400MHz) $\delta$ 1.01-1.16 (1H, m), 1.66-1.73 (2H, m), 1.74-1.82 (3H, m), 2.07-2.17 (1H, m), 2.35-2.67 (2H, m), 3.17 (3H, s), 3.23-3.45 (8H, m), 6.92 (2H, br), 7.00 (1H, d, J = 5.5 Hz), 7.08 (2H, br), 8.41 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 379 $[M + H]^+$;

Anal. Calcd for $C_{18}H_{26}N_4SO_3$: C, 57.12; H, 6.92; N, 14.80; S, 8.47. Found: C, 56.94; H, 6.77; N, 14.68; S, 8.42;

$[\alpha]^{20}_D$: +79.2° (C = 1.16, MeOH).

(Example 150) 3-amino-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]-6-methylthieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-68)

(150a) {1-[(3S)-3-(methoxymethyl)piperidin-1-yl]ethylidene}malononitrile

A methanol (5 ml) solution of (1-ethoxyethylidene)malononitrile (136 mg, 1 mmol) which was produced in Example 75 (75a) was blended with (3S)-3-(methoxymethyl)piperidine hydrochloride (166 mg, 1 mmol) which was produced in Example 147 (147b) and triethylamine (139 µL, 1 mmol) and the resultant mixture was stirred at room temperature for 15 hours. The reaction liquid was concentrated and the residue was blended with ethyl acetate (10 ml) and washed with water (10 ml) twice, and the solvent was evaporated under reduced pressure after drying the washed solution over sodium sulfate. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate =1:1) and the title compound was obtained (169 mg, yield 77%).

Pale yellow liquid

IR (KBr) $\nu_{max}$ 2933, 2206, 1563, 1417, 1110, 967, 616 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.39-1.49 (1H, m), 1.62-1.72 (1H, m), 1.83-1.99 (3H, m), 2.29 (3H, s), 3.13 (1H, dd, J = 9.8, 13.3 Hz), 3.23 (1H, dd, J = 7.3, 9.3 Hz), 3.32 (3H, s), 3.31-3.34 (2H, m), 4.01-4.14 (2H, m);

MS (EI) m/z: 219 [$M^+$], 204, 186, 174, 172, 147, 135, 134, 122, 119, 78, 67, 45, 41, 39.

(150b){(2E)-3-(dimethylamino)-1-[(3S)-3-(methoxymethyl)piperidin-1-yl]but-2-enylidene} malononitrile

A xylene (7 ml) solution of {1-[(3S)-3-(methoxymethyl)piperidin-1-yl]ethylidene}malononitrile (1.13 g, 5.2 mmol) which was produced in Example 150 (150a) was blended with N,N-dimethylacetamide dimethylacetal (7 ml) and the resultant mixutre was heated under reflux for three hours. Ethyl acetate (50 ml) was added to the residue which was obtained by concentrating the reaction liquid and the organic layer was washed with water (50 ml) twice, and the solvent was evaporated under reduced pressure after drying the washed solution over sodium sulfate. The obtained residue was purified by silica gel column chromatography (100% ethyl acetate) and the title compound was obtained (1.37 g, yield 91%).

Yellow paste-like material

IR (film) $\nu_{max}$ 2929, 2195, 1562, 1508, 1441, 1625, 1127, 1026, 758, 550 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.31-1.39 (1H, m), 1.59-1.68 (1H, m), 1.76-1.90 (3H, m), 2.22 (3H, s), 2.92-2.98 (2H, m), 3.01 (6H, s), 3.27 (2H, t, J = 7.0 Hz), 3.31 (3H, s), 3.90-3.96 (2H, m), 4.37 (1H, s);

MS (EI) m/z: 288 [$M^+$], 273, 248, 243, 223, 212, 189, 160, 146, 135, 128, 85, 70, 56, 44, 42.

(150c) 2-chloro-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]-6-methylnicotinonitrile

A methanol (15 ml) solution of {(2E)-3-(dimethylamino)-1-[(3S)-3-(methoxymethyl)piperidin-1-yl]but-2-enylidene}malononitrile (1.37 g, 4.8 mmol) which was produced in Example 150 (150b) was blended with oxalyl chloride (3.5 ml, 48 mmol) at 0°C and the resultant mixture was heated under reflux for 10 minutes. A sodium hydrogen carbonate aqueous solution (50 ml) was added to the residual substance which was obtained by concentrating the reaction liquid and the aqueous layer was extracted with ethyl acetate (20 ml) twice. After the extract was dried over sodium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate =3:1) and the title compound was obtained (1.00 g, yield 75%).
Yellow liquid
IR (film) $\nu_{max}$ 2929, 2857, 2218, 1590, 1511, 1449, 1215, 1126, 966, 855, 593 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.27-1.37 (1H, m), 1.66-1.77 (1H, m), 1.80-1.88 (2H, m), 1.99-2.07 (1H, m), 2.44 (3H, s), 2.90 (1H, dd, J = 9.08, 12.5 Hz), 3.10 (1H, dt, J = 3.1, 11.0 Hz), 3.25-3.35 (2H, m), 3.34 (3H, s), 3.87-3.94 (2H, m), 6.53 (1H, s);
MS (EI) m/z: 279 [$M^+$], 264, 246, 234, 232, 197, 194, 180, 168, 152, 142, 116, 115, 90, 71, 67, 45, 41.

(150d) 4-[(3S)-(methoxymethyl)piperidin-1-yl]-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile]

An ethanol (30 ml) solution of 2-chloro-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]-6-methylnicotinonitrile (1.00 g, 3.57 mmol) which was produced in Example 150 (150c) and thiourea (1.36 g, 17.9 mmol) were heated under reflux for 24 hours. The reaction liquid was concentrated and blended with water (20 ml) and the deposited crystal was filtered and the title compound was obtained (0.83 g, yield 83%).

White powder

Mp 137-145°C;

IR (KBr) $\nu_{max}$ 3366, 3267, 3183, 2216, 1618, 1543, 1453, 1310, 1209, 1093, 723, 626 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) δ 1.26-1.35 (1H, m), 1.52-1.58 (1H, m), 1.73-1.79 (2H, m), 1.83-1.90 (1H, m), 2.22 (3H, s), 2.98 (1H, dd, J = 10.6, 13.7 Hz), 3.10-3.18 (1H, m), 3.21-3.24 (2H, m), 3.23 (3H, s), 3.91-3.97 (2H, m), 6.35 (1H, s), 12.55 (1H, brs);

MS (EI) m/z: 277 [$M^+$], 262, 247, 232, 192, 178, 150, 144, 90, 71, 45.

(150e)3-amino-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]-6-methylthieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-[(3S)-(methoxymethyl)piperidin-1-yl]-6-methyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 150 (150d) and the title compound was obtained.

White powder

Mp 124-132°C;

IR (KBr) $\nu_{max}$ 3439, 3324, 3169, 2924, 1652, 1585, 1546, 1489, 1369, 1122, 1087, 476 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.10-1.19 (1H, m), 1.74-1.93 (3H, m), 2.09 (1H, brs), 2.43-2.48 (1H, m), 2.54-2.59 (1H, m), 2.59 (3H, s), 3.27-3.48 (4H, m), 3.34 (3H, s), 5.23 (2H, brs), 6.75 (1H, s), 6.97 (2H, brs);

HRMS m/z calcd for $C_{16}H_{23}O_2N_4S$ 335.1542, found 335.1538;

MS (ESI) m/z: 335 $[M+H]^+$;

Anal. Calcd for $C_{16}H_{22}N_4O_2S \cdot 1.0H_2O$: C, 54.33; H, 6.86; N, 15.90; S, 9.10. Found: C, 54.85; H, 6.55; N, 16.25; S, 8.74.

$[\alpha]^{20}_{D}$: +46.9° (C = 1.00, MeOH).

(Example 151) 3-amino-4-{3-(4-hydroxybutoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-105)

(151a) tert-butyl 3-{[4 -(benzyloxy)butoxy]methyl}piperidine-1-carboxylate

Sodium hydride (55% oily, 464 mg, 10.6 mmol) was suspended in tetrahydrofuran (15 mL) under nitrogen atmosphere and an N,N-dimethylformamide (6 mL) solution of tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate (Bioorg.Med.Chem.Lett. 8, (1998) 1595-1600) (1.91 g, 8.87 mmol) was added dropwise thereto. After being stirred at room temperature for one hour, the resultant mixture was blended dropwise with tetrahydrofuran (9 mL) solution of benzyl 3-bromobutyl ether (2.5 mL, 13.31 mmol) and the mixture was stirred at room temperature overnight. A saturated ammonium chloride solution was added to the reaction liquid and the resultant liquid was extracted with ethyl acetate. The organic layer was washed with water and a saturated saline solution, and the solvent was evaporated after drying the washed solution over sodium sulfate. The obtained residue was subjected to silica gel column chromatography (ethyl acetate/hexane) and the title compound was obtained (1.60 g, 48%) as a colourless oil.

IR (Liquid film) $\nu_{max}$ 2932, 2856, 1694, 1423, 1366, 1266, 1152, 1115 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 500MHz) :δ 1.14-1.23 (1H, m), 1.45 (9H, s), 1.60-1.71 (5H, m), 1.73-1.81 (2H, m), 2.58 (1H, br), 2.79 (1H, t, J=12.2 Hz), 3.25 (2H, dd, J=1.7, 6.1 Hz), 3.38-3.42 (2H, m), 3.49 (2H, t, J=6.1 Hz), 3.89 (2H, d, J=13.2 Hz), 3.98 (1H, dd, J=5.5, 11.0 Hz), 4.50 (2H, s), 7.26-7.30 (2H, m), 7.32-7.35 (3H, m);

MS(FAB) m/z: 378 $[M + H]^+$.

(151b) tert-butyl 3-[(4-hydroxybutoxy)methyl]piperidine-1-carboxylate

tert-butyl 3-{[4-(benzyloxy)butoxy]methyl}piperidine-1-carboxylate (1.71 g, 4.53 mmol) which was produced in Example 151 (151a) was dissolved in ethanol (10 mL) and the resultant solution was blended with palladium hydroxide (200 mg) and the mixture was stirred at room temperature under normal pressure hydrogen atmosphere for two hours. The reaction liquid was filtered with Celite and the solvent was evaporated under reduced pressure and the title compound was obtained (1.30 g, yield 100%) as an oil.

IR (Liquid film) $\nu_{max}$ 3741, 2976, 2935, 2859, 1745, 1694, 1426, 1268, 1242, 1154 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) :δ 1.16-1.25 (1H, m), 1.45 (9H, s), 1.40-1.50 (2H, m), 1.60-1.69 (5H, m), 1.75-1.82 (2H, m), 2.78-2.84 (1H, m), 3.29 (2H, d, J=6.3 Hz), 3.41-3.47 (2H, m), 3.64 (2H, t, J=5.7 Hz), 3.81-3.91 (2H, br), 3.97 (1H, dd, J=5.5, 11.0 Hz);

MS(FAB) m/z: 288 $[M + H]^+$.

(151c) 4-(piperidin-3-ylmethoxy)butyl acetate

tert-butyl 3-[(4-hydroxybutoxy)methyl]piperidine-1-carboxylate (775 mg, 2.70 mmol) which was produced in Example (151b) was blended with 4N hydrochloric acid - ethyl acetate solution (5 mL) and the resultant mixture was stirred at room temperature for 2.5 hours. After the reaction terminated, the residue which was obtained by evaporating the solvent was blended with methylene chloride and 1N aqueous solution of sodium hydroxide and partitioned. The obtained organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure, and the title compound was obtained (516 mg, 83%) as an oil.

$^1H$ NMR($CDCl_3$, 500MHz) :δ 1.06-1.15 (1H, m), 1.41-1.51 (1H, m), 1.59-1.85 (8H, m), 2.05 (3H, s), 2.33 (1H, dd, J=10.0, 12.2 Hz), 2.55 (1H, dt, J=2.9, 12.2 Hz), 3.00

(1H, d, J=11.7 Hz), 3.12 (1H, d, J=10.7 Hz), 3.22-3.24 (2H, m), 3.38-3.43 (2H, m), 4.08 (2H, t, J=6.6 Hz);
MS(FAB) m/z: 230 $[M + H]^+$.

(151d) 4-([1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]methoxy)butyl acetate

4-(piperidin-3-ylmethoxy)butyl acetate (504 mg, 2.20 mmol) which was produced in Example 151 (151c) was dissolved in N,N-dimethylformamide (2 mL) and the mixture was blended with (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J.Org.Chem. (1962), 27,2433-2439) (299 mg, 1.76 mmol) and the mixture was stirred at room temperature for 30 minutes. The reaction liquid was blended with N,N-dimethylformamide dimethylacetal (294 μL, 2.20 mmol) and the mixture was stirred at room temperature overnight and the mixture was stirred at 80°C for one hour. After the reaction terminated, the reaction liquid was diluted with water and extracted with ethyl acetate. The obtained organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (methylene chloride/methanol =40:1 to 20:1) and an oil (135 mg) mainly containing the title compound was obtained.
$^1$H NMR($CDCl_3$, 400MHz) :δ 1.36-1.44 (1H, m), 1.57-1.74 (6H, m), 1.83-1.91 (2H, m), 2.05 (3H,s), 3.09 (1H, dd, J=10.0, 13.1 Hz), 3.25-3.45 (7H, m), 4.08 (2H, t, J=6.6 Hz), 6.29 (1H, d, J=7.4 Hz), 7.27 (1H, d, J=7.4 Hz), 11.9 (1H, br).

(151e) 3-amino-4-{3-[(4-hydroxybutoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

4-([1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]methoxy)butyl acetate (134 mg) which was produced in Example 151 (151d) was

dissolved in N,N-dimethylformamide (1.5 mL) and the resultant solution was blended with 2-chloroacetamide (44.8 mg, 0.479 mmol) and 8N aqueous solution of sodium hydroxide (0.3 mL) and the mixture was stirred at room temperature overnight. After the reaction terminated, the reaction liquid was diluted with water and extracted with ethyl acetate. The obtained organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by thin layer chromatography (methylene chloride/methanol =10:1) and the title compound was obtained (42.2 mg, yield 30% from 4-(piperidin-3-ylmethoxy)butyl acetate) as a pale yellow solid.

Mp 140-141°C;

IR (KBr) $\nu_{max}$ 3436, 3325, 3183, 2933, 2859, 1651, 1581, 1501, 1373, 1347 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500MHz) :δ 1.09-1.18 (1H, m), 1.64-1.69 (4H, m), 1.76-1.84 (1H, m), 1.86-1.94 (2H, br), 2.08-2.17 (1H, m), 2.35 (1H, br s), 2.41 (1H, t, J=11.2 Hz), 2.64 (1H, t, J=10.5 Hz), 3.28-3.34 (1H, m), 3.36-3.51 (4H, m), 3.52-3.58 (1H, m), 3.64 (2H, d, J=2.4 Hz), 5.32 (2H, br s), 6.89 (1H, d, J=5.4 Hz), 6.98 (2H, br s), 8.46 (1H, d, J=5.4 Hz);

MS(FAB) m/z: 379 $[M + H]^+$;

Anal. calcd for $C_{18}H_{26}N_4O_3S \cdot 3/10H_2O$ : C,56.32; H,6.98; N,14.59; S,8.35. Found C,56.33; H,6.71; N,14.60, S,8.31.

(Example 152) 3-amino-4-{3-[(3-hydroxypropoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-102)

(152a) benzyl 3-{[3-(benzyloxy)propoxy]methyl}piperidine-1-carboxylate

The reaction was performed following a method described in Example 151 (151a) using benzyl 3-(hydroxymethyl)piperidine-1-carboxylate (Arch.Pharm.(Weinheim Ger.) 323,1990,9-12) (2.03 g, 8.14 mmol) in place of tert-

butyl 3-(hydroxymethyl)piperidine-1-carboxylate and using benzyl 4-bromopropyl ether in place of benzyl 3-bromobutyl ether and the title compound was obtained (538 mg, yield 17%) as an oil.

IR (Liquid film) $\nu_{max}$ 3462, 2932, 2859, 1699, 1433, 1262, 1237, 1113 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) :δ 1.14-1.24 (1H, m), 1.45 (1H, br s), 1.60-1.68 (1H, m), 1.71-1.80 (2H, m), 1.85 (2H, qu, J=6.3 Hz), 2.64 (1H, br d), 2.81-2.88 (1H, m), 3.25 (2H, d, J= 5.5 Hz), 3.43-3.49 (2H, m), 3.51-3.57 (2H, m), 3.98 (1H, dt, J=3.9, 12.9 Hz), 4.06 (1H, br s), 4.47 (2H, s), 5.10 (2H, d, J=3.9 Hz), 7.23-7.35 (10H, m);

MS(FAB) m/z: 398 $[M + H]^+$.

(152b) benzyl 3-{[3-(benzyloxy)propoxy]methyl}piperidine-1-carboxylate

benzyl 3-{[3-(benzyloxy)propoxy]methyl}piperidine-1-carboxylate (1.90 g, 4.78 mmol) which was produced in Example 152 (152a) was dissolved in ethanol (3 mL) and the resultant solution was blended with 10% palladium-carbon (180 mg) and the mixture was stirred at room temperature under normal pressure hydrogen atmosphere for 1.5 hours. After the reaction terminated, the reaction liquid was filtered with Celite and the solvent was evaporated under reduced pressure. The obtained residual substance (1.24 g) was dissolved in methylene chloride (7 mL) and the mixture was blended with di-tert-butyl dicarbonate (1.28 mL, 5.57 mmol) and the mixture was stirred at room temperature under nitrogen atmosphere for 2.5 hours. After the reaction liquid was concentrated under reduced pressure, the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate =3:1) and the title compound was obtained (1.62 g, yield 95%) as an oil.

IR (Liquid film) $\nu_{max}$ 2975, 2931, 2858, 1694, 1424, 1366, 1267, 1242, 1179, 1118 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) :δ 1.12-1.26 (1H, m), 1.45 (9H, s), 1.60-1.66 (1H, m), 1.71-1.80 (2H, m), 1.84-1.90 (2H, qu, J=6.3 Hz), 2.57 (1H, br), 2.77 (1H, t, J=11.4

Hz), 3.25 (2H, m), 3.45-3.51 (2H, m), 3.55 (2H, t, J=6.3 Hz), 3.88 (2H, dt, J=3.7, 12.5 Hz), 3.97 (1H, br), 4.49 (2H, s), 7.24-7.28 (2H, m), 7.30-7.32 (3H, m);
MS(FAB) m/z: 364 $[M + H]^+$.

(152c) tert-butyl 3-[(3-hydroxypropoxy)methyl]piperidine-1-carboxylate

The reaction was performed following a method described in Example 151 (151b) using benzyl 3-{[3-(benzyloxy)propoxy]methyl}piperidine-1-carboxylate (1.61 g, 4.43 mmol) which was produced in Example 152 (152b) and the title compound was obtained (1.17 g, yield 96%) as a colourless solid.
Mp 78°C;
IR (KBr) $\nu_{max}$ 3466, 2974, 2938, 2861, 1679, 1473, 1438, 1272, 1156, 1121 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 400MHz) :δ 1.18-1.27 (1H, m), 1.45 (9H, s), 1.56-1.66 (1H, m), 1.67-1.83 (5H, m), 2.36 (1H, br), 2.78 (2H, br), 2.92 (1H, br), 3.26-3.33 (2H, m), 3.54-3.63 (2H, m), 3.77 (2H, br), 3.86 (1H, d, J=12.1 Hz);
MS(FAB) m/z: 274 $[M + H]^+$;
Anal. calcd for $C_{14}H_{27}NO_4 \cdot 1/10H_2O$ : C,61.11; H,9.96; N,5.09. Found C, 61.05; H,10.03; N,4.99.

(152d) 3-(piperidin-3-ylmethoxy)propyl acetate

The reaction was performed following a method described in Example 151 (151c) using tert-butyl 3-[(3-hydroxypropoxy)methyl]piperidine-1-carboxylate (932 mg, 3.41 mmol) which was produced in Example 152 (152c) and the title compound was obtained (655 mg, yield 89%) as an oil.
IR (Liquid film) $\nu_{max}$ 3315, 2930, 2856, 1739, 1368, 1244, 1125, 1052 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 500MHz) :δ 1.06-1.15 (1H, m), 1.41-1.51 (1H, m), 1.62-1.69 (1H, m), 1.72-1.85 (3H, m), 1.86-1.91 (2H, m), 2.05 (3H, s), 2.33 (1H, t, J=11.3 Hz), 2.55

(1H, t, J=12.1 Hz), 3.00 (1H, d, J=12.1 Hz), 3.11 (1H, d, J=11.3 Hz), 3.24 (2H, d, J=5.9 Hz), 3.44-3.48 (2H, m), 4.15 (2H, t, J=6.4 Hz);
MS(EI) m/z: 215 $M^+$.

(152e) 4-([1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl)methoxy)propyl acetate

The reaction was performed following a method described in Example 151 (151d) using 3-(piperidin-3-ylmethoxy)propyl acetate (640 mg, 2.97 mmol) which was produced in Example 152 (152d) and an oil (234 mg) mainly containing the title compound was obtained.
$^1$H NMR($CDCl_3$, 400MHz) :δ 1.35-1.46 (1H, m), 1.57-1.74 (4H, m), 1.83-1.92 (2H, m), 2.05 (3H,s), 3.09 (1H, dd, J=9.8, 13.2 Hz), 3.26-3.50 (7H, m), 4.14 (2H, t, J=6.7 Hz), 6.29 (1H, d, J=7.8 Hz), 7.27 (1H, d, J=7.8 Hz), 11.9 (1H, br).

(152f) 3-amino-4-{3-[(3-hydroxypropoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 151 (151e) using 4-([1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]methoxy)propyl acetate which was produced in Example 152 (152d) and the title compound was obtained (109 mg, yield 10.0% from 3-(piperidin-3-ylmethoxy)propyl acetate) as a pale brown solid.
Mp 166-168°C;
IR (KBr) $\nu_{max}$ 3436, 3325, 3180, 2931, 2859, 1652, 1581, 1501, 1373, 1347 $cm^{-1}$;
$^1$H NMR($CDCl_3$, 400MHz) :δ 1.09-1.18 (1H, m), 1.76-1.86 (3H, m), 1.86-1.94 (2H, br), 2.08-2.17 (1H, m), 2.31-2.36 (1H, m), 2.42 (1H, t, J=11.5 Hz), 2.62 (1H, t, J=11.5 Hz), 3.31-3.45 (3H, m), 3.48-3.54 (1H, m), 3.55-3.66 (2H, m), 3.75 (2H, q,

J=5.5 Hz), 5.33 (2H, br s), 6.86 (1H, d, J=5.5 Hz), 6.93 (2H, br s), 8.44 (1H, d, J=5.5 Hz);

MS(FAB) m/z: 365 $[M + H]^+$;

Anal. calcd for $C_{17}H_{24}N_4O_3S \cdot 4/5H_2O$ : C,53.89; H,6.81; N,14.79; S,8.46. Found C,53.93; H,6.51; N,14.76, S,8.22.

(Example 153) 3-amino-4-[3-(3-hydroxypropyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-96)

(153a) 3-piperidin-3-ylpropyl acetate

The reaction was performed following a method described in Example 151 (151c) using tert-butyl 3-(3-hydroxypropyl)piperidine-1-carboxylate (626 mg, 2.57 mmol) which was synthesized according to a method described in J. Med. Chem. (1996), 41,2709-2719 and the title compound was obtained (400 mg, yield 84%) as an oil.

IR (Liquid film) $\nu_{max}$ 3321, 2930, 2852, 1738, 1547, 1451, 1367, 1244, 1051, 1037 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) :δ 0.96-1.06 (1H, m), 1.15-1.28 (2H, m), 1.35-1.49 (2H, m), 1.53-1.70 (4H, m), 1.78-1.86 (1H, m), 2.04 (3H, s), 2.23 (1H, t, J=11.0 Hz), 2.52 (1H, dt, J=2.7, 12.0 Hz), 2.97-3.04 (2H, m), 4.03 (2H, t, J=6.9 Hz);

MS(FAB) m/z: 186 $[M + H]^+$.

(153b) 3-[1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]propyl acetate

The reaction was performed following a method described in Example 151 (151d) using 3-piperidin-3-ylpropyl acetate (400 mg, 2.16 mmol) which was produced in Example 153 (153a) and an oil (80 mg) mainly containing the title compound was obtained.

$^1$H NMR($CDCl_3$, 400MHz) :δ 1.19-1.42 (3H, m), 1.63-1.77 (4H, m), 1.84-1.92 (1H, m), 2, 1.94-2.01 (1H, m), 2.05 (3H,s), 2.85 (1H, dd, J=10.6, 13.2 Hz), 3.12-3.19 (1H, m), 4.05 (2H, dt, J=2.0, 6.5 Hz), 4.12 (2H, t, J=12.5 Hz), 6.25 (1H, d, J=7.4 Hz), 7.29 (1H, d, J=7.4 Hz), 12.2 (1H, br).

(153c) 3-amino-4-[3-(3-hydroxypropyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 151 (151e) using 3-[1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]propyl acetate which was produced in Example 153 (153b) and the title compound was obtained (68.0 mg, yield 9.4% from 3-piperidin-3-ylpropyl acetate) as yellow amorphous.

IR (KBr) $\nu_{max}$ 3440, 3326, 3189, 2931, 2852, 1648, 1581, 1502, 1373, 1346 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400MHz) :δ 0,98-1.08 (1H, m), 1.30-1.36 (2H, m), 1.54-1.82 (4H, m), 1.84-2.03 (3H, m), 2.28 (1H, t, J=11.2 Hz), 2.62 (1H, t, J=11.2 Hz), 3.38 (2H, t, J=9.6 Hz), 3.65 (2H, t, J=6.3 Hz), 5.52 (2H, br s), 6.84 (1H, d, J=5.1 Hz), 6.97 (2H, br s), 8.41 (1H, d, J=5.1 Hz);

MS(FAB) m/z: 335 $[M + H]^+$.

(Example 154) 3-amino-4-[3-(3-methoxypropyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-109)

(154a) tert-butyl 3-(3-methoxy propyl)piperidine-1-carboxylate

tert-butyl 3-(3-hydroxypropyl)piperidine-1-carboxylate (J. Med. Chem. (1996), 41, 2709-2719) (617 mg, 2.54 mmol) was dissolved in tetrahydrofuran (10 mL) and the resultant solution was blended with sodium hydride (55% oily, 230 mg, 5.27 mmol) and the mixture was stirred under nitrogen atmosphere at room temperature for 30 minutes. The reaction liquid was blended with methyl iodide

(0.60 mL, 9.64 mmol) and the mixture was stirred at room temperature for 30 minutes. Furthermore, the reaction liquid was blended with sodium hydride (200 mg, 4.58 mmol) and methyl iodide (1.2 mL, 19.2 mmol) and after it was stirred at room temperature for one hour, was further blended with a saturated ammonium chloride aqueous solution and the mixture was extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 6:1) and the title compound was obtained (618 mg, yield 95%) as an oil.

IR (Liquid film) $\nu_{max}$ 2976, 2933, 2856, 1696, 1423, 1366, 1267, 1241, 1177, 1150 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500MHz) :δ 1.02-1.11 (1H, m), 1.18-1.32 (2H, m), 1.36-1.49 (2H, m), 1.45 (9H, s), 1.57-1.66 (3H, m), 1.77-1.86 (1H, m), 2.30-2.60 (1H, br), 2.74 (1H, t, J=11.7 Hz), 3.33 (3H, s), 3.36 (2H, t, J=6.6 Hz), 3.92 (1H, d, J=12.7 Hz), 3.80-4.10 (1H, br);

MS(EI) m/z: 257 $M^+$.

(154b) 3-(3-methoxy propyl)piperidine

The reaction was performed following a method described in Example 151 (151c) using tert-butyl 3-(3-methoxypropyl)piperidine-1-carboxylate (607 mg, 2.36 mmol) which was produced in Example 154 (154a) and the title compound was obtained (362 mg, yield 98%) as an oil.

IR (Liquid film) $\nu_{max}$ 3401, 3311, 2929, 2852, 2737, 1645, 1543, 1451, 1274, 1118 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) :δ 0.96-1.06 (1H, m), 1.13-1.28 (2H, m), 1.35-1.49 (2H, m), 1.53-1.67 (3H, m), 1.79-1.86 (2H, m), 2.22 (1H, t, J=11.0 Hz), 2.51 (1H, dt, J=2.5, 11.8 Hz), 2.96-3.06 (2H, m), 3.32 (3H, s), 3.34 (2H, t, J=6.7 Hz);

MS(FAB) m/z: 158 $[M + H]^+$.

(154c) 4-[3-(3-methoxypropyl)piperidin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

3-(3-methoxypropyl)piperidine (355 mg, 2.26 mmol) which was produced in Example 154 (154b) was dissolved in N,N-dimethylformamide (2 mL) and the resultant solution was blended with (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J.Org.Chem. (1962), 27,2433-2439) (312 mg, 1.83 mmol) and the mixture was stirred at room temperature for one hour. The reaction liquid was blended with N,N-dimethylformamide dimethylacetal (266 μL, 1.99 mmol), stirred at room temperature overnight and then diluted with water and the aqueous layer was extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 30:1-20:1) and thin layer chromatography (100% ethyl acetate) and the title compound was obtained (59.6 mg, yield 9.0%) as a yellow amorphous substance.
IR (KBr) $\nu_{max}$ 3115, 2935, 2854, 2209, 1624, 1552, 1519, 1310, 1250, 1116 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 400MHz) :δ 1.18-1.28 (1H, m), 1.29-1.40 (2H, m), 1.55-1.75 (4H, m), 1.83-1.90 (1H, m), 1.94-2.02 (1H, m), 2.85 (1H, dd, J=10.8, 13.1 Hz), 3.14-3.21 (1H, m), 3.33 (3H, s), 3.36-3.41 (2H, m), 4.08-4.18 (2H, m), 6.27 (1H, d, J=7.4 Hz), 7.30 (1H, d, J=7.4 Hz), 12.23 (1H, br);
MS(FAB) m/z: 292 $[M + H]^+$.

(154d) 3-amino-4-[3-(3-methoxypropyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide

4-[3-(3-methoxypropyl)piperidin-1-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile (58.6 mg, 0.201 mmol) which was produced in Example 154 (154c) was dissolved in N,N-dimethylformamide (1 mL) and the resultant solution was blended with 2-chloroacetamide (32.8 mg, 0.350 mmol) and 8N aqueous solution of sodium hydroxide (0.2 mL) and the mixture was stirred at room temperature for two hours. After the reaction terminated, the reaction liquid was diluted with water and extracted with ethyl acetate. The obtained organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by thin layer chromatography (100% ethyl acetate) and the title compound was obtained (65.5 mg, yield 93%) as yellow amorphous.

IR (KBr) $\nu_{max}$ 3438, 3323, 3178, 2932, 2852, 1651, 1580, 1556, 1501, 1371 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) : $\delta$ 0,98-1.08 (1H, m), 1.29-1.35 (2H, m), 1.56-1.68 (2H, m), 1.69-1.82 (2H, m), 1.84-1.92 (1H, m), 1.93-2.01 (1H, m), 2.31 (1H, t, J=11.0 Hz), 2.62 (1H, t, J=11.7 Hz), 3.32 (3H, s), 3.35-3.42 (2H, m), 3.37 (2H, t, J=6.5 Hz), 5.29 (2H, br s), 6.85 (1H, d, J=5.5 Hz), 6.99 (2H, br s), 8.43 (1H, d, J=5.5 Hz);

MS(FAB) m/z: 349 $[M + H]^+$;

Anal. calcd for $C_{17}H_{24}N_4O_2S \cdot 1/5H_2O$ : C,58.00; H,6.99; N,15.91; S, 9.11. Found C,58.06; H,6.98; N,15.70; S,8.85.

(Example 155) 3-amino-4-[3-(4-hydroxybutyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-97)

(155a) tert-butyl 3-(3-oxopropyl)piperidine-1-carboxylate

tert-butyl 3-(3-hydroxypropyl)piperidine-1-carboxylate (J. Med. Chem. (1996), 41,2709-2719) (1.08 g, 4.44 mmol) was dissolved in methylene chloride (10 mL) and the resultant solution was blended with Dess-Martin periodinane (2.3 g, 5.42 mmol) and the mixture was stirred under nitrogen atmosphere at room

temperature for two hours. Ether was added to the reaction liquid and the organic layer was washed sequentially with 1N aqueous solution of sodium hydroxide and a saturated saline solution and dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure and the title compound was obtained (1.00 g, yield 93%).

IR (Liquid film) $\nu_{max}$ 2976, 2932, 2857, 1726, 1692, 1425, 1366, 1268, 1174, 1150 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500MHz) :δ 1.05-1.14 (1H, m), 1.37-1.60 (4H, m), 1.45 (9H, s), 1.60-1.67 (1H, m), 1.78-1.85 (1H, m), 2.40-2.60 (1H, br), 2.49 (2H, t, J=7.3 Hz), 2.80 (1H, t, J=11.2 Hz), 3.88 (1H, dt, J=3.5, 13.1 Hz), 3.98 (1H, br), 9.79 (1H, s);

MS(FAB) m/z: 242 $[M + H]^+$.

(155b) tert-butyl 3-[(3)-4-methoxybut-3-enyl]piperidine-1-carboxylate

(Methoxymethyl) triphenylphosphonium chloride (1.76 g, 5.13 mmol) was dissolved in tetrahydrofuran (5 mL) and the resultant solution was blended with a hexane solution (1.50M, 3.0 mL, 4.5 mmol) of N-butyllithium under ice-cooling and the mixture was stirred under nitrogen atmosphere at 0°C for 30 minutes. A tetrahydrofuran (5 mL) solution of tert-butyl 3-(3-oxopropyl)piperidine-1-carboxylate (675 mg, 2.80 mmol) which was produced in Example 155 (155a) was added dropwise to the reaction mixture and the resultant mixture was stirred at 0°C for one hour and the mixture was stirred at room temperature for 3 hours. A saturated ammonium chloride aqueous solution was added to the reaction liquid and the aqueous layer was extracted with ethyl acetate. The obtained organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate =8:1) and the title compound was obtained (475 mg, yield 63%) as an oil.

IR (Liquid film) $\nu_{max}$: 2976, 2932, 2853, 1695, 1656, 1423, 1366, 1267, 1176, 1109 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) : $\delta$ 0.98-1.12 (1H, br), 1.15-1.33 (2H, m), 1.37-1.56 (2H, m), 1.45 (9H, s), 1.58-1.66 (1H, m), 1.76-1.87 (1H, m), 1.95 (1H, q, J=7.0 Hz), 2.08 (1H, dq, J=1.3, 7.5 Hz), 2.26-2.63 (1H, br), 2.75 (1H, t, J= 10.8 Hz), 3.49 (3/2H, s), 3.56 (3/2H, s), 3.74-4.07 (1H, br), 3.85-3.92 (1H, m), 4.30 (1/2H, q, J=7.0 Hz), 4.68 (1/2H, dt, J=7.5, 12.5 Hz), 5.85 (1/2H, d, J=6.3 Hz), 6.27 (1/2H, d, J= 12.5 Hz);
MS(EI) m/z: 269 $M^+$.

(155c) tert-butyl 3-(4-hydroxybutyl)piperidine-1-carboxylate

tert-butyl 3-[(3)-4-methoxybut-3-enyl]piperidine-1-carboxylate (465 mg, 1.73 mmol) which was produced in Example 155 (155b) was dissolved in methanol (2 mL) and water (2 mL) and the resultant solution was blended with sulfuric acid (0.2 mL) and the mixture was stirred under nitrogen atmosphere at room temperature for seven hours. The reaction liquid was blended with a sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate. The extract was concentrated under reduced pressure and the obtained residue was dissolved in acetone (4 mL), and the resultant solution was blended with amberlite (IR - 120PLUS, 1 g), and the mixture was stirred overnight at room temperature. The reaction liquid was filtered and the filtrate was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure and a crude aldehyde compound (237 mg) was obtained. The obtained compound was dissolved in methanol (5 mL) and the solution was blended with an excess amount of sodium borohydride under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature for 30 minutes. The reaction liquid was blended with water and then a saturated ammonium chloride aqueous solution and extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous sodium sulfate

and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate =3:1) and the title compound was obtained (197 mg, yield 44%) as an oil.

IR (Liquid film) $\nu_{max}$ 3443, 2976, 2932, 2859, 1694, 1672, 1428, 1367, 1269, 1152 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500MHz) : δ 1.03-1.11 (1H, m), 1.14-1.33 (3H, m), 1.35-1.47 (4H, m), 1.45 (9H, s), 1.52-1.65 (3H, m), 1.78-1.84 (1H, m), 2.48 (1H, br), 2.77-2.82 (1H, m), 3.64 (2H, q, J=5.4 Hz), 3.71-4.04 (2H, br);

MS(EI) m/z: 257 $M^+$.

(155d) 4-piperidin-3-ylbutyl acetate

The reaction was performed following a method described in Example 151 (151c) using tert-butyl 3-(4-hydroxybutyl)piperidine-1-carboxylate (301 mg, 1.17 mmol) which was produced in Example 155 (155c) and the title compound was obtained (195 mg, yield 84%) as an oil.

IR (Liquid film) $\nu_{max}$ 3323, 2930, 2851, 1739, 1645, 1459, 1445, 1367, 1243, 1038 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) : δ 0.95-1.05 (1H, m), 1.12-1.25 (2H, m), 1.31-1.49 (4H, m), 1.57-1.66 (3H, m), 1.69-1.85 (2H, m), 2.04 (3H, s), 2.21 (1H, dd, J=10.5, 12.0 Hz), 2.52 (1H, dt, J=2.7, 12.0 Hz), 2.96-3.05 (2H, m), 4.04 (2H, t, J=6.7 Hz);

MS(EI) m/z: 198 $(M - H)^+$.

(155e) 4-[1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]butyl acetate

The reaction was performed following a method described in Example 151 (151d) using 4-piperidin-3-ylbutyl acetate (185 mg, 0.928 mmol) which was produced in Example 155 (155d) and an oil (36 mg) mainly containing the title compound was obtained.

$^1$H NMR($CDCl_3$, 500MHz) :δ 1.16-1.50 (5H, m), 1.59-1.78 (4H, m), 1.84-2.00 (2H, m), 2.06 (3H, s), 3.13-3.19 (1H, m), 3.49-3.55 (1H, m), 4.07 (2H, t, J=6.4 Hz), 4.09-4.15 (2H, m), 6.25 (1H, d, J=7.8 Hz), 7.31 (1H, d, J=7.8 Hz), 12.1 (1H, br).

(155f) 3-amino-4-[3-(4-hydroxybutyl)piperidin-1-yl]thieno-[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 151 (151e) using 4-[1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]butyl acetate which was produced in Example 155 (155e) and the title compound was obtained (15.5 mg, yield 4.8% from 4-piperidin-3-ylbutyl acetate) as a yellow amorphous substance.

IR (KBr) $\nu_{max}$ 3441, 3326, 3187, 2931, 2855, 1649, 1581, 1502, 1374, 1247 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 500MHz) :δ 0,99-1.07 (1H, m), 1.25-1.33 (2H, m), 1.36-1.50 (3H, m), 1.54-1.69 (2H, m), 1.70-1.81 (2H, m), 1.85-1.91 (1H, m), 1.96 (1H, d, J=11.7 Hz), 2.29 (1H, t, J=11.0 Hz), 2.64 (1H, t, J=11.7 Hz), 3.40 (2H, t, J=11.0 Hz), 3.65 (2H, t, J=6.6 Hz), 5.34 (2H, br s), 6.87 (1H, d, J=5.1 Hz), 7.01 (2H, br s), 8.45 (1H, d, J=5.1 Hz);

MS(FAB) m/z: 349 $[M + H]^+$.

(Example 156) 3-amino-4-{3-[(2-cyanoethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-152)

(156a) benzyl 3-[(2-cyanoethoxy)methyl]piperidine-1-carboxylate

benzyl 3-(hydroxymethyl)piperidine-1-carboxylate (Arch.Pharm.(Weinheim Ger.) 323,1990,9-12) (6.30 g, 25.3 mmol) was dissolved in tetrahydrofuran (50 mL) and the resultant solution was blended with acrylonitrile (3.31 mL, 50.5 mmol) and sodium hydroxide (160 mg, 2.85 mmol) and the mixture was stirred under nitrogen atmosphere at room temperature for nine hours. Furthermore, the reaction liquid

was blended with sodium hydroxide (160 mg, 2.85 mmol) and the mixture was stirred at room temperature overnight. Water was added to the reaction liquid and the aqueous layer was extracted with ethyl acetate. After the extract was washed with a saturated saline, it was dried over anhydrous sodium sulfate solution and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate =3:1 to 2:1) and the title compound was obtained (6.91 g, yield 90%).

IR (Liquid film) $\nu_{max}$ 2937, 2863, 2251, 1698, 1471, 1433, 1262, 1236, 1155, 1117 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) :δ 1.22-1.33 (1H, m), 1.40-1.53 (1H, m), 1.62-1.70 (1H, m), 1.76-1.87 (2H, br), 2.55 (2H, br s), 2.66-2.87 (1H, br), 2.93 (1H, t, J=11.0 Hz), 3.35 (2H, d, J=5.1 Hz), 3.59 (2H, br s), 3.92 (1H, dt, J=4.2, 13.3 Hz), 4.01 (1H, br s), 5.08-5.17 (2H, m), 7.27-7.35 (5H, m);

MS(EI) m/z: 303 $[M + H]^+$.

(156b) 3-(piperidin-3-ylmethoxy) propanenitrile

Hydrogenolysis reaction was performed using benzyl 3-[(2-cyanoethoxy)methyl]piperidine-1-carboxylate (1.03 g, 3.40 mmol) which was produced in Example 156 (156a) in the presence of a palladium-carbon catalyst in ethanol and the title compound was obtained (564 mg, yield 99%) as an oil.

IR (Liquid film) $\nu_{max}$ 3389, 3326, 2932, 2860, 2251, 1640, 1545, 1418, 1273, 1113 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) :δ 1.08-1.18 (1H, m), 1.40-1.51 (1H, m), 1.62-1.69 (2H, m), 1.75-1.83 (2H, m), 2.36 (1H, dd, J=10.0, 11.7 Hz), 2.55 (1H, dd, J=2.7, 11.7 Hz), 2.59 (2H, t, J=6.4 Hz), 2.99 (1H, dt, J=3.3, 12.1 Hz), 3.12 (1H, d, J=12.1 Hz), 3.32 (2H, d, J=6.3 Hz), 3.58-3.67 (2H, m);

MS(FAB) m/z: 169 $[M + H]^+$.

(156c) 4-(3-[(2-cyanoethoxy)methyl]piperazin-1-yl)-2-thioxo-1,-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 151 (151d) using 3-(piperidin-3-ylmethoxy)propanenitrile (550 mg, 3.27 mmol) which was produced in Example 156 (156b) and an oil (178 mg) mainly containing the title compound was obtained.

$^1$H NMR($CDCl_3$, 400MHz) :δ 1.38-1.48 (1H, m), 1.67-1.91 (3H, m), 2.03-2.11 (1H, m), 2.61-2.64 (2H, m), 3.15 (1H, dd, J=9.8, 13.3 Hz), 3.33-3.41 (2H, m), 3.47 (1H, dd, J=4.7, 9.8 Hz), 3.60-3.66 (2H, m), 4.08 (2H, t, J=14.5 Hz), 6.33 (1H, d, J=7.8 Hz), 7.33 (1H, d, J=7.8 Hz), 12.2 (1H, br).

(156d) 3-amino-4-{3-[(2-cyanoethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 151 (151e) using 4-(3-[(2-cyanoethoxy)methyl]piperazin-1-yl)-2-thioxo-1,-dihydropyridine-3-carbonitrile which was produced in Example 156 (156c) and the title compound was obtained (42.8 mg, yield 3.6% from 3-(piperidin-3-ylmethoxy)propanenitrile) as a yellow solid.

Mp 155-156°C;

IR (KBr) $\nu_{max}$ 3439, 3330, 3169, 2932, 2250, 1649, 1580, 1501, 1371, 1346 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 400MHz) :δ 1.11-1.26 (1H, m), 1.72-1.97 (3H, m), 2.12 (1H, br s), 2.48 (1H, t, J=11.2 Hz), 2.54-2.64 (1H, m), 2.59 (2H, t, J=6.1 Hz), 3.34-3.50 (4H, m), 3.60-3.69 (2H, m), 5.46 (2H, br s), 6.87 (1H, d, J=4.9 Hz), 6.96 (2H, br s), 8.44 (1H, d, J=4.9 Hz);

MS(FAB) m/z: 360 $[M + H]^+$;

Anal. calcd for $C_{17}H_{21}N_5O_2S \cdot 1/2H_2O$ : C,55.42; H,6.02; N,19.01; S,8.70. Found C,55.44; H,6.00; N,18.88, S,8.48.

(Example 157) 3-amino-4-(3-{[3-(dimethylamino)propoxy]methyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-144)

(157a) benzyl 3-[(3-aminopropoxy)methyl]piperidine-1-carboxylate

benzyl 3-[(2-cyanoethoxy)methyl]piperidine-1-carboxylate (2.06 g, 6.81 mmol) which was produced in Example 156 (156a) was dissolved in methanol (30 mL) and the resultant solution was blended with cobalt (II) chloride (excess amount) and sodium borohydride (excess amount) divided into several times and the mixture was stirred under nitrogen atmosphere at 0°C for 3.5 hours. The reaction liquid was blended with water and methylene chloride and partitioned. The obtained organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate =1:1 to 0:1) and the title compound was obtained (1.31 g, yield 63%) as an oil.

IR (Liquid film) $\nu_{max}$ 2935, 2858, 1699, 1470, 1432, 1261, 1236, 1154, 1116, 699 $cm^{-1}$;

$^1H$ NMR($CD_3OD$, 400MHz) :δ 1.20-1.32 (1H, m), 1.38-1.51 (1H, m), 1.62-1.81 (5H, m), 2.55-2.83 (3H, m), 2.92 (1H, br s), 3.20-3.33 (2H, m), 3.38-3.51 (2H, m), 3.91 (1H, d, J=13.3 Hz), 4.04 (1H, d, J=12.5 Hz), 5.09 (2H, s), 7.26-7.33 (5H, m);

MS(FAB) m/z: 307 $[M + H]^+$.

(157b) benzyl 3-{[3-(dimethylamino)propoxy]methyl}piperidine-1-carboxylate

benzyl 3-[(3-amino propoxy)methyl]piperidine-1-carboxylate (890 mg, 2.90 mmol) which was produced in Example 157 (157a) was mixed with formic acid (5 mL) and formaldehyde (5 mL) and the mixture was stirred under nitrogen

atmosphere at 100°C for two hours. After the reaction liquid was diluted with ethyl acetate and washed with water, it was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure and the title compound was obtained (933 mg, 96%) as an oil.

IR (Liquid film) $\nu_{max}$ 2939, 2858, 1700, 1469, 1432, 1366, 1261, 1236, 1154, 1117 $cm^{-1}$;

$^1H$ NMR($CD_3OD$, 400MHz) :δ 1.19-1.30 (1H, m), 1.38-1.50 (1H, m), 1.62-1.81 (5H, m), 2.15-2.27 (6H, br), 2.31-2.45 (2H, m), 2.60-2.84 (2H, br), 2.91 (1H, t, J=12.3 Hz), 3.20-3.28 (1H, m), 3.34-3.46 (2H, m), 3.93 (1H, br s), 4.03-4.09 (1H, m), 5.09 (2H, s), 7.25-7.34 (5H, m);

MS(FAB) m/z: 335 $[M + H]^+$.

(157c) N,N-dimethyl-N-[3-(piperidin-3-ylmethoxy)propyl]amine

Hydrogenolysis reaction was performed using benzyl 3-{[3-(dimethylamino)propoxy]methyl}piperidine-1-carboxylate (926 mg, 2.79 mmol) which was produced in Example 157 (157b) in the presence of a palladium-carbon catalyst in ethanol and the title compound was obtained (535 mg, yield 96%) as an oil.

IR (Liquid film) $\nu_{max}$ 3400, 2936, 2858, 2796, 1655, 1544, 1468, 1273, 1164, 1115 $cm^{-1}$;

$^1H$ NMR($CD_3OD$, 400MHz) :δ 1.10-1.21 (1H, m), 1.6-1.58 (1H, m), 1.66-1.83 (5H, m), 2.24 (6H, s), 2.33 (1H, dd, J=10.6, 12.1 Hz), 2.35-2.42 (2H, m), 2.53 (1H, dt, J=3.1, 12.1 Hz), 2.98 (1H, d, J=13.3 Hz), 3.09 (1H, d, J=12.1 Hz), 3.20-3.30 (2H, m), 3.39-3.47 (2H, m);

MS(EI) m/z: 200 $[M^+]$.

(157d) 4-(3-([3-(dimethylamino)propoxy]methyl)piperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 151 (151d) using N,N-dimethyl-N-[3-(piperidin-3-ylmethoxy)propyl]amine (520 mg, 2.60 mmol) which was produced in Example 157 (157c) and an oil (78.7 mg) mainly containing the title compound was obtained.

$^1$H NMR($CDCl_3$, 400MHz) :δ 1.34-1.42 (1H, m), 1.70-1.90 (6H, m), 2.23 (3H, s), 2.25 (3H, s), 2.38 (2H, t, J=7.4), 3.08 (1H, dd, J=9.8, 13.1 Hz), 3.23-3.48 (5H, m), 4.02-4.14 (2H, m), 6.30 (1H, d, J=7.4 Hz), 7.34 (1H, d, J=7.4 Hz), 7.86 (1H, br).

(157e) 3-amino-4-(3-{[3-(dimethylamino)propoxy]methyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 151 (151e) using 4-(3-([3-(dimethylamino)propoxy]methyl)piperidin-1-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 157 (157d) and the title compound was obtained (44.1 mg, yield 4.3% from N,N-dimethyl-N-[3-(piperidin-3-ylmethoxy)propyl]amine) as a yellow solid.

Mp 174°C;

IR (KBr) $\nu_{max}$ 3450, 3311, 3167, 2936, 2858, 1649, 1579, 1504, 1368, 1345 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 500MHz) :δ 1.08-1.20 (1H, m), 1.70-1.86 (3H, m), 1.86-1.95 (2H, m), 2.10 (1H, br s), 2.21 (6H, s), 2.32 (2H, t, J=7.3 Hz), 2.46 (1H, t, J=10.7 Hz), 2.59 (1H, t, J=11.2 Hz), 3.27-3.39 (2H, m), 3.41-3.50 (4H, m), 5.30 (2H, br s), 6.90 (1H, d, J=5.4 Hz), 7.01 (2H, br s), 8.46 (1H, d, J=5.4 Hz);

MS(FAB) m/z: 392 $[M + H]^+$.

(Example 158) 3-amino-4-{3-[(cyanomethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-149)

(158) benzyl 3-[(cyanomethoxy)methyl]piperidine-1-carboxylate

benzyl 3-(hydroxymethyl)piperidine-1-carboxylate (Arch. Pharm. (Weinheim Ger.) 323, 1990, 9-12) (1.01 g, 4.05 mmol) was dissolved in tetrahydrofuran (10 mL), and the resultant solution was blended with sodium hydride (55% oily, 216 mg, 4.95 mmol) under ice-cooling and the mixture was stirred under nitrogen atmosphere at room temperature for 30 minutes. A tetrahydrofuran (7 mL) solution of bromoacetonitrile (0.38 mL, 5.67 mmol) was added dropwise to the reaction liquid for more than two hours. The reaction liquid was blended with water after stirring at room temperature for two hours, and the mixture was extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate =5:1 to 4:1) and the title compound was obtained (655 mg, yield 56%) as an oil.

IR (Liquid film) $\nu_{max}$ 3469, 2939, 2862, 1698, 1471, 1434, 1263, 1236, 1155, 1110 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) :$\delta$ 1.23-1.33 (1H, m), 1.41-1.54 (1H, m), 1.62-1.71 (1H, m), 1.75-1.90 (2H, m), 2.90-2.97 (1H, m), 2.69-2.87 (1H, br), 3.38-3.50 (2H, m), 3.94-4.10 (1H, br), 3.93 (1H, dt, J=4.0, 13.4 Hz), 4.18 (2H, br s), 5.07-5.18 (2H, m), 7.27-7.37 (5H, m);

MS(EI) m/z: 289 $[M + H]^+$.

(158b) (piperidin-3-ylmethoxy)acetonitrile

benzyl 3-[(cyanomethoxy)methyl]piperidine-1-carboxylate (732 mg, 2.54 mmol) which was produced in Example 158 (158a) was dissolved in ethanol (4 mL), and the resultant solution was blended with ammonium acetate (106 mg, 1.38 mmol) and 10% palladium-carbon (90 mg) and the mixture was stirred at room temperature under normal pressure hydrogen atmosphere for 1.5 hours. The reaction liquid was

filtered with Celite after the reaction terminated and the solvent was evaporated under reduced pressure. The residue was dissolved in methylene chloride, washed with 1N aqueous solution of sodium hydroxide and then with a saturated saline solution and dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the title compound was obtained (294 mg, yield 75%) as an oil.
IR (Liquid film) $\nu_{max}$ 3323, 2929, 2856, 2810, 2742, 1470, 1443, 1357, 1271, 1106 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 400MHz) :δ 1.10-1.20 (1H, m), 1.41-1.52 (1H, m), 1.62-1.72 (2H, m), 1.74-1.85 (2H, m), 2.36 (1H, dd, J=9.8, 11.7 Hz), 2.55 (1H, dt, J=3.1, 11.7 Hz), 2.99 (1H, dt, J=3.5, 12.0 Hz), 3.08-3.12 (1H, m), 3.38-3.45 (2H, m), 4.22 (2H, s);
MS(FAB) m/z: 155 $[M + H]^+$.

(158c) 4-{3-[(cyanomethoxy)methyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 151 (151d) using (piperidin-3-ylmethoxy)acetonitrile (292 mg, 1.89 mmol) which was produced in Example 158 (158b) and an oil (111 mg) mainly containing the title compound was obtained.
$^1H$ NMR($CDCl_3$, 500MHz) :δ 1.32-1.42 (1H, m), 1.70-1.93 (4H, m), 3.42-3.59 (4H, m), 4.08-4.15 (2H, m), 4.29 (2H, s), 6.29 (1H, d, J=7.5 Hz), 7.36 (1H, d, J=7.5 Hz), 12.2 (1H, br).

(158d) 3-amino-4-{3-[(cyanomethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 151 (151e) using 4-{3-[(cyanomethoxy)methyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 158 (158c) and the

title compound was obtained (11.4 mg, yield 1.7% from (piperidin-3-ylmethoxy)acetonitrile) as a yellow solid.

Mp 217-218°C;

IR (KBr) $\nu_{max}$ 3426, 3328, 3156, 2932, 1649, 1581, 1504, 1371, 1346, 1111 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400MHz) :δ 1.13-1.25 (1H, m), 1.75-1.87 (1H, m), 1.88-1.96 (2H, m), 2.11-2.22 (1H, br), 2.47 (1H, t, J=11.0 Hz), 2.61 (1H, t, J=11.0 Hz), 3.40-3.58 (4H, m), 4.24 (2H, s), 5.28 (2H, br s), 6.88 (1H, d, J=5.5 Hz), 6.96 (2H, br s), 8.45 (1H, d, J=5.5 Hz);

MS(FAB) m/z: 346 $[M + H]^+$;

Anal. calcd for $C_{16}H_{19}N_5O_2S \cdot 7/10H_2O$ : C,53.68; H,5.74; N,19.56; S,8.96. Found C,53.67; H,5.56; N,19.34, S,8.96.

(Example 159) 3-amino-4-{3-[(2-hydroxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-99)

(159a) benzyl 3-[(2-tert-butoxy-2-oxoethoxy)hydroxymethyl]piperidine-1-carboxylate

50% aqueous solution of sodium hydroxide (18 mL) divided into several times was added to a benzene (18 mL) suspension of benzyl 3-(hydroxymethyl)piperidine-1-carboxylate (Arch. Pharm. (Weinheim Ger.), 323, 1990, 9-12) (11.97 g, 48.01 mmol), tert-butyl bromoacetate (16.3 mL, 110 mmol) and tetra-N-butylammonium bisulfate (3.8 g, 11 mmol) under ice-cooling. The reaction mixture was stirred at 0°C for 15 minutes and stirred further overnight at room temperature and the resultant solution was blended with ethyl acetate (30 mL) and partitioned. The organic layer was washed with a saturated saline solution (3x60 mL) and after drying over sodium sulfate, it was filtered and concentrated. The obtained residue was purified by silica gel column chromatography (hexane: ethyl acetate =5:1 to 4:1) and the title compound was obtained (16.88 g, yield 96%).

Colourless liquid

IR (film) $\nu_{max}$ 3033, 2935, 2858, 1747, 1701, 1431, 1368, 1260, 1232, 1138, 979, 850, 734, 699 $cm^{-1}$;

$^1H$ NMR($CDCl_6$, 400 MHz) $\delta$ 1.28 (1H, br s), 1.47 (10H, s), 1.67 (1H, br s), 1.84 (2H, br s), 2.76 (1H, br s), 2.88 (1H, t, J = 10.3 Hz), 3.30-3.44 (2H, br m), 3.92 (2H, s), 3.98 (1H, br s), 4.10 (1H, br s), 5.13 (2H, s), 7.27-7.39 (5H, m);

HRMS m/z: found $[M + H]^+$ 364.2111, calcd for $C_{20}H_{30}NO_5$ $[M + H]^+$ 364.2124.

(159b) ({1-[(benzyloxy)carbonyl]piperidin-3-yl}methoxy)acetic acid

A methylene chloride solution (30 mL) of benzyl 3-[(2-tert-butoxy-2-oxoethoxy)hydroxymethyl]piperidine-1-carboxylate (5.04 g, 13.9 mmol) which was produced in Example 159 (159a) was ice-cooled and blended with trifluoroacetic acid (10 mL). The reaction mixture was stirred at 0°C for 15 minutes and after further stirring overnight at room temperature, it was concentrated. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate =6:4 to 1:5) and the title compound was obtained (3.86 g, yield 91%).

Colourless liquid

IR (film) $\nu_{max}$ 3065, 2937, 1698, 1441, 1263, 1139, 977, 699 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.24-1.40 (1H, m), 1.41-1.56 (1H, m), 1.57-1.72 (1H, m), 1.73-2.00 (2H, m), 2.78-3.30 (2H, m), 3.31-3.48 (2H, m), 3.57-4.15 (4H, m), 5.13 (2H, br s), 7.27-7.40 (5H, m);

MS (FAB) m/z: 308 $[M+H]^+$, 264, 246, 176.

(159c) benzyl 3-[(2-hydroxymethoxy)methyl]piperidine-1-carboxylate

Boron trifluoride ether complex (3.5 mL, 27.7 mmol) was slowly added dropwise to a tetrahydrofuran (20 mL) suspension of sodium borohydride (0.785 g, 20.8 mmol) under ice-cooling and the mixture was stirred under nitrogen atmosphere

for 30 minutes. A tetrahydrofuran (22 mL) solution of ({1-[(benzyloxy)carbonyl]piperidin-3-yl}methoxy)acetic acid (5.317 g, 17.3 mmol) which was produced in Example 159 (159b) was added dropwise to the reaction mixture and after it was stirred at 0°C for 3 hours, it was blended with methanol (5 mL). Insolubles were filtered by Celite and washed with ethyl acetate (100 mL). The crude product which was obtained by concentrating the filtrate was purified by silica gel column chromatography (hexane:ethyl acetate =6: 4 to 100% ethyl acetate) and the title compound was obtained (4.546 g, yield 90%).

Colourless liquid

IR (film) $\nu_{max}$ 3446, 2933, 1698, 1435, 1261, 1154, 1072, 699 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.20-1.34 (1H, m), 1.40-1.55 (1H, m), 1.57-1.72 (1H, m), 1.74-1.94 (2H, m), 2.75-3.15 (2H, m), 3.29-3.37 (2H, m), 3.42-3.60 (2H, m), 3.64-4.03 (4H, m), 5.12 (2H, br s), 7.25-7.37 (5H, m);

MS (FAB) m/z: 294 $[M+H]^+$, 250, 246, 226, 165.

(159d) 2-(piperidin-3-ylmethoxy)ethanol

An ethanol (7 mL) solution of benzyl 3-[(2-hydroxymethoxy)methyl]piperidine-1-carboxylate (1.767 g, 6.02 mmol) which was produced in Example 159 (159c) was blended with 10% palladium-carbon catalyst (150 mg) under nitrogen atmosphere and the mixture was stirred under normal pressure hydrogen atmosphere for four hours. After the reaction terminated, the crude product which was obtained by removing the catalyst by Celite filtration and evaporating the solvent was purified by silica gel column chromatography (Chromatorex, (NH), Fuji Silysia Chemical LTD.) (100% ethyl acetate) and the title compound was obtained (836 mg, yield 87%).

Colourless liquid

$^1$H NMR($CDCl_6$, 400 MHz) δ 1.05-1.19 (1H, m), 1.39-1.51 (1H, m), 1.61-1.70 (1H, m), 1.73-1.86 (2H, m), 2.11 (2H, br s), 2.37 (2H, t, J = 10.2 Hz), 2.57 (2H, t, J = 11.7 Hz), 2.99 (2H, d, J = 12.1 Hz), 3.12 (2H, d, J = 12.1 Hz), 3.325 (2H, d, J = 6.3 Hz), 3.46-3.58 (2H, m), 3.69-3.77 (2H, m).

(159e) 4-{3-[(2-hydroxyethoxy)methyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

2-(piperidin-3-ylmethoxy)ethanol (749 mg, 4.70 mmol) which was produced in Example 159 (159d) and (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J. Org. Chem., (1962), 27,2433-2439) (780 mg, 4.58 mmol) were dissolved in N,N-dimethylformamide (8 mL) and the mixture was stirred at room temperature for two hours. Furthermore, N,N-dimethylformamide dimethylacetal (0.73 mL, 5.50 mmol) was added to the reaction liquid and the mixture was stirred at room temperature overnight. The residue which was obtained by concentrating the reaction mixture was purified by silica gel column chromatography (methylene chloride: methanol =98:2 to 85:15) and thin layer column chromatography (methylene chloride:methanol =98:2) and the title compound was obtained (283 mg). Yield 21%.

Amorphous

IR (film) $\nu_{max}$ 3193, 3148, 3043, 2932, 2859, 2207, 1621, 1571, 1448, 1361, 1249, 1167, 1121, 1059, 781, 599 $cm^{-1}$;

$^1$H NMR($CDCl_6$, 400 MHz) δ 1.27-1.41 (1H, m), 1.62-1.76 (1H, m), 1.86 (2H, br d, J = 9 Hz), 2.08 (1H, br s), 2.70-2.98 (1H, br s), 3.065 (1H, dd, J = 9.8, 13.3 Hz), 3.24-3.38 (2H, m), 3.445 (1H, dd, J = 4.7, 9.8 Hz), 3.48-3.60 (3H, m), 3.74 (2H, t, J = 4.7 Hz), 4.03 (2H, br d, J = 13.7 Hz), 4.325 (2H, br d, J = 13.7 Hz), 6.36 (1H, d, J = 7.4 Hz), 7.395 (1H, d, J = 7.4 Hz);

HRMS m/z: found $[M + H]^+$ 294.1254, calcd for $C_{14}H_{20}N_3O_2S$ $[M + H]^+$ 294.1276.

(159f) 3-amino-4-{3-[(2-hydroxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-{3-[(2-hydroxyethoxy)methyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 159 (159e) and the title compound was synthesized. Yield 55%.

Amorphous

IR (KBr) $\nu_{max}$ 3438, 3326, 3191, 3148, 2931, 2856, 1648, 1581, 1502, 1448, 1372, 1247, 1123, 1059, 960, 825, 737, 605 $cm^{-1}$;

$^1H$ NMR($CDCl_6$, 400 MHz) $\delta$ 1.07-1.22 (1H, m), 1.72-2.03 (4H, m), 2.15 (1H, br s), 2.46 (1H, br t, J = 10.2 Hz), 2.61 (1H, br t, J = 10.2 Hz), 3.31-3.59 (6H, m), 3.72 (2H, br s), 5.30 (2H, br s), 6.875 (1H, d, J = 5.4 Hz), 6.97 (2H, br s), 7.835 (1H, d, J = 5.4 Hz);

HRMS m/z: found $[M + H]^+$ 351.1496, calcd for $C_{16}H_{23}N_4O_3S$ $[M + H]^+$ 351.1490.

(Example 160) tert-butyl 2-({1-[3-amino-2-(aminocarbonyl)thieno[2,3-b]pyridin-4-yl]piperidin-3-yl}methoxy)ethylcarbamate (Exemplified Compound No. 1-182)

(160a) benzyl 3-({2-[(methylsulfonyl)oxy]ethoxy}methyl)piperidine-1-carboxylate

A methylene chloride (50 mL) solution of triethylamine (1.70 mL, 12.1 mmol), methanesulfonyl chloride (0.87 mL, 11.2 mmol) and benzyl 3-[(2-hydroxy methoxy)methyl]piperidine-1-carboxylate (2.74 g, 9.34 mmol) which was produced in Example 159 (159c) was stirred overnight under nitrogen atmosphere. After having added a saturated saline solution (15 mL), extraction of the reaction liquid was performed. The extract was dried over sodium sulfate and the crude product which was obtained by evaporating the solvent after filtration was purified by silica

gel column chromatography (hexane:ethyl acetate = 4:1 to 2:1) and the title compound was obtained (3.25 g, yield 94%).

Pale yellow liquid

IR (film) $\nu_{max}$ 2937, 1697, 1433, 1354, 1236, 1175, 1019, 922, 807 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.16-1.28 (1H, m), 1.41-1.55 (1H, m), 1.62-1.73 (1H, m), 1.74-1.87 (2H, m), 2.62-2.82 (1H, m), 2.83-3.13 (4H, m), 3.27-3.41 (2H, m), 3.64 (2H, br s), 3.93-4.17 (2H, m), 4.31 (2H, br s), 5.07-5.18 (2H, m), 7.28-7.41 (5H, m);

HRMS m/z: found $[M + H]^+$ 372.1448, calcd for $C_{17}H_{26}N_1O_6S$ $[M + H]^+$ 372.1480.

(160b) benzyl 3-[(2-azidoethoxy)methyl]piperidine-1-carboxylate

N,N-dimethylformamide (10 mL) solution of sodium azide (723 mg, 11.12 mmol) and benzyl 3-({2-[(methylsulfonyl)oxy]ethoxy}methyl)piperidine-1-carboxylate (3.178 g, 8.56 mmol) which was produced in Example 160 (160a) was heated and the mixture was stirred at 80°C for six hours. The reaction mixture was blended with ethyl acetate (50 mL) and water (20 mL) and partitioned. The organic layer was washed with a saturated saline solution (2x15 mL) and dried over sodium sulfate, and the crude product which was obtained by evaporating the solvent after filtration was purified by silica gel column chromatography (hexane:ethyl acetate =7:3) and the title compound was obtained (2.721 g, yield 100%).

Pale yellow liquid

IR (film) $\nu_{max}$ 2934, 2103, 1699, 1432, 1235, 1153, 699 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.22-1.34 (1H, m), 1.40-1.54 (1H, m), 1.62-1.72 (1H, m), 1.74-1.89 (2H, m), 2.64-2.95 (2H, m), 3.26-3.41 (4H, m), 3.53-3.63 (2H, m), 3.94-4.15 (2H, m), 5.07-5.19 (2H, m), 7.28-7.39 (5H, m);

MS (FAB) m/z: 319 $[M+H]^+$, 275, 242, 211, 183, 91, 63.

(160c) benzyl 3-({2-[(tert-butoxycarbonyl)amino]ethoxy}methyl)piperidine-1-carboxylate

A tetrahydrofuran (8 mL) solution of benzyl 3-[(2-azidoethoxy)methyl]piperidine-1-carboxylate (2.635 g, 8.28 mmol) which was produced in Example 160 (160b) was blended with triphenylphosphine (2.280 g, 8.69 mmol) and the mixture was stirred at room temperature for 20 hours. The reaction liquid was blended with water (0.3 mL) and the mixture was stirred for 20 hours and then blended with di-tert-butyl dicarbonate (1.987 g, 9.10 mmol) and the mixture was stirred for a further 40 hours. The crude product which was obtained by concentrating the reaction mixture was purified by silica gel column chromatography (hexane:ethyl acetate =8:2) and the title compound was obtained (3.218 g, yield 99%).

Colourless oil

IR (film) $\nu_{max}$ 3355, 2933, 2861, 1701, 1520, 1433, 1260, 1237, 1155, 1121, 985, 867, 764, 699 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.17-1.30 (1H, m), 1.44 (10H, s), 1.58-1.70 (1H, m), 1.72-1.83 (1H, m), 2.75 (1H, br s), 2.92 (1H, t, J = 10.9 Hz), 3.28 (4H, d, J = 5.9 Hz), 3.37-3.48 (2H, m), 3.87-4.06 (2H, m), 4.68-5.05 (1H, m), 5.12 (2H, m), 7.25-7.37 (5H, m);

HRMS m/z: found $[M + H]^+$ 393.2429, calcd for $C_{21}H_{29}N_{10}O_2$ $[M + H]^+$ 393.2389.

(160d) tert-butyl 2-(piperidin-3-ylmethoxy)ethyl carbamate

An ethanol (14 mL) solution of benzyl 3-({2-[(tert-butoxycarbonyl)amino]ethoxy}methyl)piperidine-1-carboxylate (3.158 g, 8.04 mmol) which was produced in Example 160 (160c) was blended with 10% palladium-carbon catalyst (257 mg) under nitrogen atmosphere and the mixture was stirred overnight under normal pressure hydrogen atmosphere. The catalyst was

removed by Celite filtration and it was washed with ethanol. The crude product which was obtained by concentrating the filtrate was purified by silica gel column chromatography (Chromatorex (NH), Fuji Silysia Chemical LTD.) (100% ethyl acetate) and the title compound was obtained (2.018 g, yield 97%).

A white solid

IR (film) $\nu_{max}$ 3303, 3205, 2978, 2939, 2857, 2804, 1690, 1560, 1367, 1275, 1170, 1126, 979, 949, 869, 777, 608 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.03-1.16 (1H, m), 1.44 (9H, s), 1.56-1.69 (2H, br s), 1.70-1.81 (2H, br s), 2.32 (1H, t, J = 10.9 Hz), 2.54 (1H, t, J = 10.9 Hz), 2.99 (1H, d, J = 12.2 Hz), 3.10 (1H, d, J = 12.2 Hz), 3.20-3.32 (4H, m), 3.43 (2H, br s), 4.86 (1H, br s);

HRMS m/z: found $[M + H]^+$ 259.1998, calcd for $C_{13}H_{27}N_2O_3$ $[M + H]^+$ 259.2021.

(160e) tert-butyl 2-(piperidin-3-ylmethoxy)ethylcarbamate

The reaction was performed following a method described in Example 146 (146c) using tert-butyl [2-(piperidin-3-ylmethoxy)ethyl]carbamate which was produced in Example 160 (160d) and the title compound was obtained. Yield 44%.

Pale yellowish white amorphous

IR (KBr) $\nu_{max}$ 3344, 3190, 3130, 2974, 2933, 2861, 2208, 1703,1620, 1515, 1450, 1365, 1302, 1249, 1170, 1167, 1120, 999, 964, 856, 781 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.30-1.40 (1H, m), 1.44 (9H, s), 1.63-1.74 (1H, br s), 1.80-1.91 (2H, br d), 2.02 (1H, br s), 3.00-3.10 (1H, m), 3.22-3.33 (4H, m), 3.38-3.50 (3H, m), 4.03-4.17 (2H, m), 4.89 (1H, br s), 6.28 (1H, d, J = 7.0 Hz), 7.28 (1H, d, J = 7.0 Hz);

HRMS m/z: found $[M + H]^+$ 393.1998, calcd for $C_{19}H_{29}N_4O_3S$ $[M + H]^+$ 393.1960.

(160f) tert-butyl 2-({1-[3-amino-2-(aminocarbonyl)thieno[2,3-b]pyridin-4-yl]piperidin-3-yl}methoxy)ethylcarbamate

The reaction was performed following a method described in Example 5 (5c) using tert-butyl 2-(piperidin-3-ylmethoxy)ethylcarbamate which was produced in Example 160 (160e) and the title compound was synthesized. Yield 79%.

Pale yellow amorphous

IR (KBr) $\nu_{max}$ 3440, 3326, 3186, 2973, 2931, 2859, 1706, 1648, 1581, 1502, 1451, 1367, 1248, 1169, 1122, 1056, 995, 961, 865, 736, 557 $cm^{-1}$;

$^1H$ NMR($CDCl_6$, 400 MHz) $\delta$ 1.05-1.22 (1H, m), 1.42 (9H, s), 1.71-1.95 (3H, m), 2.10 (1H, br s), 2.46 (1H, br t, J = 10.2 Hz), 2.59 (1H, br t, J = 10.2 Hz), 3.21-3.55 (8H, m), 4.82 (1H, br s), 5.33 (2H, br s), 6.90 (1H, d, J = 5.5 Hz), 6.99 (2H, br s), 8.46 (1H, d, J = 5.5 Hz);

HRMS m/z: found $[M + H]^+$ 450.2160, calcd for $C_{21}H_{32}N_5O_4S$ $[M + H]^+$ 450.2175.

(Example 161) 3-amino-4-{3-[(2-aminoethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide dihydrochloride (Exemplified Compound No. 1-133)

tert-butyl 2-({1-[3-amino-2-(aminocarbonyl)thieno[2,3-b]pyridin-4-yl]piperidin-3-yl}methoxy)ethylcarbamate (259 mg, 0.58 mmol) which was produced in Example 160 was suspended in 1,4-dioxane (4 mL) and was blended with 4N hydrochloric acid-ethyl acetate (3 mL) and the mixture was stirred overnight. The solvent was evaporated and the obtained yellow solid was dried under reduced pressure and the title compound was obtained.

IR (KBr) $\nu_{max}$ 3309, 3169, 2967, 2932, 2859, 1649, 1513, 1482, 1385, 1257, 1107, 1044, 963, 803, 729, 555, 476 $cm^{-1}$;

$^1H$ NMR($CD_3OD$, 400 MHz) $\delta$ 1.31-1.46 (1H, m), 1.75-1.95 (3H, m), 2.20 (1H, br s), 3.02-3.18 (3H, m), 3.20-3.31 (1H, m), 3.38-3.50 (2H, m), 3.57-3.70 (2H, m), 3.92

(1H, br d, J = 12.5 Hz), 4.04 (1H, br d, J = 12.5 Hz), 7.23 (1H, d, J = 7.0 Hz), 8.35 (1H, d, J = 7.0 Hz);

HRMS m/z: found 350.1657 $[M - 2HCl + H]^+$, calcd for $C_{16}H_{24}N_5O_2S$ $[M - 2HCl + H]^+$ 350.1650.

(Example 162) 3-amino-4-(3-{[2-(dimethylamino)-2-oxoethoxy]methyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-155)

(162a) benzyl 3-{2-[(dimethylamino)-2-oxoethoxy]methyl}piperidine-1-carboxylate

A methylene chloride (25 mL) solution of ({1-[(benzyloxy)carbonyl]piperidin-3-yl}methoxy)acetic acid (1.062 g, 3.45 mmol) which was produced in Example 159 (159b) was blended with triethylamine (0.53 mL, 3.8 mmol) and ethyl chloroformate (0.36 mL, 3.8 mmol) under ice-cooling and the mixture was stirred for one hour. Furthermore, triethylamine (0.6 mL, 4.32 mmol) and dimethylamine hydrochloride (352 mg, 3.8 mmol) were added to the reaction liquid and it was stirred for one hour and then stirred overnight at room temperature. A saturated saline solution (15 mL) was added to the reaction mixture, and extraction was performed and the extracted organic layer was dried over sodium sulfate and the crude product which was obtained by concentrating the organic layer after filtration was purified by silica gel column chromatography (hexane:ethyl acetate =1:1) and the title compound was obtained (961 mg, yield 83%).

Pale yellow liquid

IR (film) $\nu_{max}$ 3567, 3495, 2934, 2858, 1698, 1664, 1498, 1432, 1260, 1235, 1152, 1113, 980, 764, 700 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.17-1.32 (1H, m), 1.46 (1H, br s), 1.60-1.72 (1H, m), 1.75-1.91 (2H, m), 2.72 (1H, br s), 2.81-3.09 (7H, m), 3.27-3.44 (2H, m), 3.86-4.13 (4H, m), 4.68-5.05 (2H, m), 5.04-5.16 (2H, m), 7.25-7.37 (5H, m);

HRMS m/z: found $[M + H]^+$ 335.1964, calcd for $C_{17}H_{28}N_2O_4$ $[M + H]^+$ 335.1970.

(162b) N,N-dimethyl-2-(piperidin-3-ylmethoxy) acetamide

An ethanol (7 mL) solution of benzyl 3-{2-[(dimethylamino)-2-oxoethoxy]methyl}piperidine-1-carboxylate (936 mg, 2.80 mmol) which was produced in Example 162 (162a) was blended with 10% palladium-carbon (102.2 mg) and the mixture was stirred overnight under normal pressure hydrogen atmosphere. Palladium was removed by Celite filtration and it was washed with ethanol. The crude product which was obtained after concentration of the filtrate was purified by silica gel column chromatography (Chromatorex, (NH), Fuji Silysia Chemical LTD.) (100% ethyl acetate) and the title compound was obtained (506 mg, yield 90%).

Pale yellow liquid

IR (film) $\nu_{max}$ 3460, 3309, 2930, 2854, 1651, 1505, 1447, 1404, 1346, 1265, 1109, 1023, 886, 859, 806, 709, 574 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.07-1.17 (1H, m), 1.38-1.51 (1H, m), 1.61-1.80 (1H, m), 1.70-1.86 (2H, m), 2.36 (1H, dd, J = 9.8, 11.7 Hz), 2.54 (1H, dt, J = 2.7, 11.7 Hz), 2.94 (3H, s), 2.97 (1H, br s), 3.01 (3H, s), 3.14 (1H, br d, J = 12.1 Hz), 3.29-3.36 (2H, m), 4.10 (2H, s);

HRMS m/z: found $[M + H]^+$ 201.1611, calcd for $C_{10}H_{21}N_2O_2$ $[M + H]^+$ 201.2890.

(162c) 2-{[1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]methoxy}-N,N-dimethylacetamide

N,N-dimethyl-2-(piperidin-3-ylmethoxy)acetamide which was produced in Example 162 (162b) (5.695 g, 28.44 mmol) and (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J. Org. Chem., (1962), 27, 2433-2439) (4.825 g, 28.34 mmol) were suspended in ethanol (100 mL) and the mixture was stirred at room temperature for 13 hours. After the solvent was evaporated, N,N-dimethylformamide (60 mL) and

N,N-dimethylformamide dimethylacetal (4.16 mL, 31.27 mmol) were added and the mixture was stirred overnight at room temperature. The crude product which was obtained by concentrating the reaction mixture was purified by silica gel column chromatography (methylene chloride:methanol =98:2 to 85:15) and the title compound was obtained (2.455 g). Yield 26%.

Light greenish white amorphous

IR (KBr) $\nu_{max}$ 3138, 3036, 2933, 2858, 2206, 1649,1618, 1511, 1446, 1300, 1244, 1170, 1164, 1113, 1004, 964, 855, 782 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.29-1.43 (1H, m), 1.59-1.81 (3H, m), 1.99-2.12 (2H, m), 2.95 (3H, s), 2.97 (3H, s), 3.07-3.11 (1H, m), 3.21-3.31 (1H, m), 3.36-3.53 (2H, m), 4.05-4.18 (4H, m), 6.32 (1H, d, J = 7.4 Hz), 7.31 (1H, d, J = 7.4 Hz);

HRMS m/z: found $[M + H]^+$ 335.1545, calcd for $C_{16}H_{23}N_4O_2S$ $[M + H]^+$ 335.1541.

(162d) 3-amino-4-(3-{[2-(dimethylamino)-2-oxoethoxy]methyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 2-{[1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]methoxy}-N,N-dimethylacetamide which was produced in Example 162 (162c) and the title compound was synthesized. Yield 79%.

A pale brown solid

IR (KBr) $\nu_{max}$ 3436, 3324, 3187, 2930, 2855, 1646, 1579, 1501, 1466, 1371, 1354, 1248, 1118, 1058, 961, 825, 737, 475 $cm^{-1}$;

$^1H$ NMR($CDCl_6$, 400 MHz) $\delta$ 1.07-1.24 (1H, m), 1.68-1.95 (3H, m), 2.15 (1H, br s), 2.42-2.64 (2H, m), 2.93 (3H, s), 2.98 (3H, s), 3.32-3.57 (4H, m), 4.12 (2H, s), 5.27 (2H, br s), 6.90 (1H, d, J = 5.5 Hz), 6.87 (2H, br s), 8.43 (1H, d, J = 5.5 Hz);

HRMS m/z: found $[M + H]^+$ 392.1754, calcd for $C_{18}H_{26}N_5O_3S$ $[M + H]^+$ 392.1756;

Anal. Calcd for $C_{18}H_{25}N_5O_3S \cdot H_2O$: C,52.79; H,6.65; N,17.10. Found: C,53.12; H,6.25; N,17.27.

(Example 163) 3-amino-4-(3-{[2-(diethylamino)-2-oxoethoxy]methyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-164)

(163a) benzyl 3-{2-[(diethylamino)-2-oxoethoxy]methyl}piperidine-1-carboxylate

A methylene chloride (30 mL) solution of ({1-[(benzyloxy)carbonyl]piperidin-3-yl}methoxy)acetic acid (920 mg, 2.99 mmol) which was produced in Example 159 (159b) was blended with triethylamine (0.44 mL, 3.14 mmol) and ethyl chloroformate (0.3 mL, 3.14 mmol) under ice-cooling. After the reaction liquid was stirred for one hour, diethylamine (0.61 mL, 5.98 mmol) was added to the reaction liquid and the mixture was stirred for 30 minutes and the mixture was stirred overnight at room temperature. A saturated saline solution (15 mL) was added to the reaction liquid, and extraction was performed and the extracted organic layer was dried over sodium sulfate and the crude product which was obtained by concentrating the organic layer after filtration was purified by silica gel column chromatography (hexane:ethyl acetate =1:1) and the title compound was obtained (958 mg, yield 88%).

Colourless liquid

IR (film) $\nu_{max}$ 3553, 3496, 2935, 2858, 1698, 1664, 1468, 1433, 1261, 1235, 1153, 1115, 983, 765, 699 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.04-1.32 (7H, m), 1.46 (1H, br s), 1.58-1.74 (1H, m), 1.82 (2H, br s), 2.71 (1H, br s), 2.86 (1H, br t, J = 10.9 Hz), 3.16-3.46 (6H, m), 3.96 (1H, br s), 4.06 (3H, br s), 5.02-5.18 (2H, m), 7.22-7.37 (5H, m);

HRMS m/z: found $[M + H]^+$ 363.2290, calcd for $C_{20}H_{31}N_2O_4$ $[M + H]^+$ 363.2283.

(163b) N,N-diethyl-2-(piperidin-3-ylmethoxy)acetamide

An ethanol (7 mL) solution of benzyl 3-{2-[(diethylamino)-2-oxoethoxy]methyl}piperidine-1-carboxylate (946 mg, 2.61 mmol) which was produced in Example 163 (163a) was blended with 10% palladium-carbon (110 mg) under nitrogen atmosphere and the mixture was stirred overnight under normal pressure hydrogen atmosphere. Palladium was removed by Celite filtration and it was washed with ethanol. The crude product which was obtained after concentration of the filtrate was purified by silica gel column chromatography (Chromatorex, (NH), Fuji Silysia Chemical LTD.) (100% ethyl acetate) and the title compound was obtained (549 mg, yield 92%).

Colourless liquid

IR (film) $\nu_{max}$ 3464, 3310, 2932, 2853, 1643, 1464, 1440, 1380, 1268, 1221, 1123, 1109, 1035, 858, 796, 590 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.08-1.22 (7H, m), 1.38-1.51 (1H, m), 1.57-1.71 (2H, m), 1.75-1.88 (2H, m), 2.36 (1H, t, J = 11.7 Hz), 2.54 (1H, t, J = 11.7 Hz), 2.99 (1H, d, J = 11.7 Hz), 3.14 (1H, d, J = 11.7 Hz), 3.28-3.43 (6H, m), 4.10 (2H, s);

MS (EI) m/z: found $[M + H]^+$ 229.19, calcd for $C_{12}H_{25}N_2O_2$ $[M + H]^+$ 229.34.

(163c) 2-{[1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]methoxy}-N,N-diethylacetamide

N,N-diethyl-2-(piperidin-3-ylmethoxy) acetamide which was produced in Example 163 (163b) (524 mg, 2.3 mmol) and (2Z)-2-cyano-3-ethoxybut-2-enethioamide (J. Org. Chem., (1962), 27,2433-2439) (389 mg, 2.3 mmol) were dissolved in N,N-dimethylformamide (100 mL) and the mixture was stirred at room temperature for 2.5 hours. The reaction liquid was blended with N,N-dimethylformamide dimethylacetal (0.365 mL, 2.8 mmol) and the mixture was stirred overnight at room temperature. The crude product which was obtained by concentrating the reaction mixture was purified by silica gel column chromatography

(methylene chloride:methanol =98:2 to 85:15) and thin layer chromatography - (methylene chloride:methanol =95:5) and a mixture (84 mg) mainly containing the title compound was obtained.

$^1$H NMR($CDCl_3$, 400 MHz) δ 1.15 (3H, t, J = 7.0 Hz), 1.21 (3H, t, J = 7.0 Hz), 1.26-1.54 (1H, m), 1.64-2.03 (3H, m), 2.03-2.06 (2H, m), 3.05-3.14 (1H, m), 3.23-3.58 (6H, m), 4.03-4.22 (4H, m), 6.38 (1H, d, J = 7.4 Hz), 7.38 (1H, d, J = 7.4 Hz).

(163d) 3-amino-4-(3-{[2-(diethylamino)-2-oxoethoxy]methyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

A mixture (84 mg) containing 2-{[1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)-piperidin-3-yl]methoxy}-N,N-diethylacetamide which was produced in Example 163 (163c) was mixed with 2-chloroacetamide (22 mg, 0.23 mmol), 8N aqueous solution of sodium hydroxide (1 mL) and N,N-dimethylformamide (1 mL) and the mixture was stirred for 3 hours. The reaction mixture was blended with ethyl acetate (25 mL) and a saturated saline solution (10 mL) and partitioned. The aqueous layer was extracted with ethyl acetate (15 mL) and after the combined organic layer was dried over sodium sulfate, it was filtered and concentrated. The obtained crude product was purified by thin layer chromatography (ethyl acetate:methanol =95:5) and the title compound was obtained (55 mg). Yield 5% from (2Z)-2-cyano-3-ethoxybut-2-enethioamide.

IR (KBr) $\nu_{max}$ 3425, 3327, 3178, 2967, 2933, 2857, 1644, 1579, 1501, 1458, 1371, 1354, 1247, 1122, 1108, 1059, 962, 823, 770, 596, 477 $cm^{-1}$;

$^1$H NMR($CDCl_6$, 400 MHz) δ 1.05-1.21 (7H, m), 1.70-1.96 (3H, m), 2.14 (1H, br s), 2.43-2.64 (2H, m), 3.20-3.59 (8H, m), 4.10 (2H, s), 5.25 (2H, br s), 6.87 (1H, d, J = 5.1 Hz), 6.97 (2H, br s), 8.43 (1H, d, J = 5.1 Hz);

HRMS m/z: found $[M + H]^+$ 420.2075, calcd for $C_{18}H_{26}N_5O_3S$ $[M + H]^+$ 420.2069.

(Example 164) 4-(3-{[2-(acetylamino)ethoxy]methyl}piperidin-1-yl)-3-aminothieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-173)

A methylene chloride (2 mL) solution of 3-amino-4-{3-[(2-aminoethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide dihydrochloride (38 mg, 0.089 mmol) which was produced in Example 161 was blended with triethylamine (46 μL, 0.331 mmol) and acetyl chloride (8 μL, 0.114 mmol) and the mixture was stirred overnight. The reaction liquid was blended with methylene chloride (10 mL) and a saturated saline solution (10 mL) and partitioned. The organic layer was dried over sodium sulfate and the crude product which was obtained by concentration after filtration was purified by thin layer chromatography (methylene chloride:methanol =96:4) and the title compound was obtained (29.3 mg, yield 84%).

Amorphous

IR (KBr) $\nu_{max}$ 3437, 3319, 3194, 2930, 2855, 1648, 1555, 1501, 1439, 1372, 1246, 1122, 1056, 996, 960, 824, 736, 475 $cm^{-1}$;

$^1H$ NMR($CDCl_6$, 400 MHz) δ 1.06-1.19 (1H, m), 1.64-2.01 (6H, m), 2.13 (1H, br s), 2.40 (1H, br t, J = 10.7 Hz), 2.64 (1H, br t, J = 10.7 Hz), 3.24-3.61 (8H, m), 5.43 (2H, br s), 5.90 (1H, br s), 6.90 (1H, d, J = 5.4 Hz), 6.99 (2H, br s), 8.47 (1H, d, J = 5.4 Hz);

HRMS m/z: found $[M + H]^+$ 392.1769, calcd for $C_{18}H_{26}N_5O_3S$ $[M + H]^+$ 392.1756.

(Example 165) 3-amino-4-(3-{[2-(hexanoylamino)ethoxy]methyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-181)

A methylene chloride (30 mL) solution of hexanoic acid (1.03 mL, 8.27 mmol), N-hydroxysuccinimide (1.0 g, 8.69 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.66 g, 8.68 mmol) was stirred overnight at room temperature. A saturated saline solution (30 mL) was added to

the reaction mixture and extraction was performed. After the extract was dried over sodium sulfate, it was filtered and concentrated and a crude product of active ester was obtained. A methylene chloride (2 mL) solution of the crude active ester (16.6 mg, 0.078 mmol) and 3-amino-4-{3-[(2-aminoethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide dihydrochloride (32.9 mg, 0.078 mmol) which was produced in Example 161 was blended with triethylamine (38 μL, 0.273 mmol) and the mixture was stirred overnight. The reaction mixutre was blended with methylene chloride (15 mL) and a saturated saline solution (5 mL) and partitioned. The organic layer was dried over sodium sulfate and the crude product which was obtained by concentration after filtration was purified by thin layer chromatography (ethylacetate:methanol =95:5) and the title compound was obtained (23.3 mg, yield 67%).

Amorphous

IR (KBr) $\nu_{max}$ 3440, 3321, 3191, 2929, 2858, 1645, 1579, 1502, 1457, 1373, 1346, 1247, 1122, 1057, 960, 824, 736, 557 $cm^{-1}$;

$^1H$ NMR($CDCl_6$, 400 MHz) δ 0.86 (3H, t, J = 7.0 Hz), 1.06-1.18 (1H, m), 1.20-1.33 (4H, m), 1.53-1.64 (2H, m), 1.72-1.96 (3H, m), 2.06-2.18 (3H, m), 2.41 (1H, br t, J = 10.7 Hz), 2.62 (1H, br t, J = 10.7 Hz), 3.25-3.56 (8H, m), 5.43 (2H, br s), 5.84 (1H, br s), 6.87 (1H, d, J = 5.1 Hz), 6.97 (2H, br s), 8.44 (1H, d, J = 5.1 Hz);

HRMS m/z: found $[M + H]^+$ 448.2383, calcd for $C_{22}H_{34}N_5O_3S$ $[M + H]^+$ 448.2382.

(Example 166) 3-amino-4-{3-[3-(2-hydroxyethoxy)propyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-101)

(166a) benzyl 3-(3-hydroxypropyl)piperidine-1-carboxylate

3-piperidine-3-ylpropan-1-ol (9.86 g, 68.8 mmol) which was synthesized with reference to J. Org. Chem., 1964, 29, 1736-1738 and triethylamine (11.5 mL, 82.6 mmol) were dissolved in methylene chloride (69 mL), and a methylene chloride (35

mL) solution of benzyl chloroformate (10.8 mL, 75.7 mmol) was added dropwise under ice-cooling. After dropwise addition was completed, the reaction liquid was stirred at room temperature for two hours, and was blended with water (70 mL) and partitioned. The aqueous layer was extracted with methylene chloride (50 mLx2), and after the combined extract was dried over magnesium sulfate, the solvent was evaporated under reduced pressure. The residual substance was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1 to 1/1) and 10.13 g of the title compound was obtained (yield 53%).

Slightly yellow oil

IR (film) $\nu_{max}$ 3445, 2935, 2857, 1699, 1435, 1261, 1238 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.01-1.72 (8H, m), 1.75-1.90 (1H, m), 2.41-2.66 (1H, m), 2.76-2.91 (1H, m), 3.54-3.69 (2H, m), 3.87-4.12 (2H, m), 5.12 (2H, br.s), 7.26-7.42 (5H, m);

MS (FAB) m/z: 278 $[M+H]^+$, 258, 242, 234.

(166b) benzyl 3-[3-(2-tert-butoxy-2-oxoethoxy)propyl]piperidine-1-carboxylate

The reaction was performed following a method described in Example 159 (159a) using benzyl 3-(3-hydroxypropyl)piperidine-1-carboxylate which was produced in Example 166 (166a) in place of benzyl 3-(3-hydroxymethyl)piperidine-1-carboxylate and the title compound was obtained.

Colourless liquid

IR (film) $\nu_{max}$ 2936, 1749, 1701, 1431, 1237, 1136 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.08-1.86 (9H, m), 1.47 (9H, s), 2.80 (1H, t, J = 11.7 Hz), 3.46-3.49 (2H, m), 3.92 (2H, s), 3.98-4.11 (3H, m), 5.10 (2H, brs), 7.26-7.33 (5H, m);

MS (FAB) m/z: 392 $[M+H]^+$, 390, 336, 258, 256, 91.

(166c) (3-{1-[(benzyloxy)carbonyl]piperidin-3-yl}propoxy)acetic acid

A methanol/water (2:1) (15 mL) suspension of benzyl 3-[3-(2-tert-butoxy-2-oxoethoxy)propyl]piperidine-1-carboxylate (1.80 g, 4.60 mmol) which was produced in Example 166 (166b) was blended with lithium hydroxide and the mixture was stirred at room temperature for 17 hours. The reaction liquid was concentrated and the residue was blended with water (100 mL) and methylene chloride (50 mL) and partitioned. The obtained aqueous layer was blended with 1N hydrochloric acid (30 mL) and extracted with methylene chloride (100 mL) three times. The organic layer were combined and the solvent was evaporated under reduced pressure after drying over sodium sulfate and a crude product (1.54 g) of the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 3065, 2937, 1760, 1698, 1440, 1263, 1137, 699 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.03-1.17 (1H, m), 1.18-1.54 (4H, m), 1.56-1.74 (3H, m), 1.76-1.89 (1H, m), 2.47-2.65 (1H, m), 2.78-2.95 (1H, m), 3.44-3.61 (2H, m), 3.90-4.11 (2H, m), 4.08 (2H, s), 5.12 (2H, s), 7.27-7.40 (5H, m);

MS (FAB) m/z: 336 [$M+H^+$], 273, 242, 226, 180.

(166d) benzyl 3-[3-(2-hydroxyethoxy)propyl]piperidine-1-carboxylate

The reaction was performed following a method described in Example 159 (159c) using (3-{1-[(benzyloxy)carbonyl]piperidin-3-yl}propoxy)acetic acid which was produced in Example 166 (166c) and the title compound was obtained.

Colourless liquid

IR (film) $\nu_{max}$ 3457, 2935, 1698, 1434, 1362, 1237, 1119, 764, 699 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.02-1.16 (1H, m), 1.18-1.36 (2H, m), 1.37-1.53 (2H, m), 1.54-1.72 (3H, m), 1.80-1.90 (1H, m), 2.40-2.65 (1H, m), 2.74-2.88 (1H, m),

3.34-3.56 (4H, m), 3.68-3.76 (2H, m), 3.89-4.18 (2H, m), 5.12 (2H, s), 7.27-7.43 (5H, m);

MS (FAB) m/z: 322 $[M+H^+]$, 278, 242, 226, 186.

(166e) 2-(3-piperidin-3-ylpropoxy)ethanol

The reaction was performed following a method described in Example 159 (159d) using benzyl 3-[3-(2-hydroxyethoxy)propyl]piperidine-1-carboxylate which was produced in Example 166 (166d) and the title compound was obtained.

Yellow liquid

IR (film) $\nu_{max}$ 3296, 2930, 1450, 1112, 893 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 0.96-1.08 (1H, m), 1.16-1.29 (2H, m), 1.39-1.50 (2H, m), 1.53-1.68 (3H, m), 1.73-1.87 (1H, m), 2.23 (1H, t, J = 10.3 Hz), 2.53 (1H, dt, J = 2.9, 12.2 Hz), 3.00 (1H, d, J = 12.2 Hz), 3.06 (1H, d, J = 11.7 Hz), 3.43-3.50 (2H, m), 3.51-3.55 (2H, m), 3.73 (2H, t, J = 4.9 Hz);

MS (FAB) m/z: 188 $[M+H]^+$, 126, 96, 44.

(166f) 4-{3-[3-(2-hydroxyethoxy)propyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed following a method described in Example 121 (121c) using 2-(3-piperidin-3-ylpropoxy)ethanol which was produced in Example 166 (166e) and the title compound was obtained.

Brown powder

Mp 112-116°C;

IR (KBr) $\nu_{max}$ 3526, 3117, 2940, 2210, 1625, 1547, 1461, 1313, 1249, 1128, 953, 800 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.17-1.46 (3H, m), 1.56-1.77 (4H, m), 1.83-1.90 (1H, m), 1.94-2.02 (1H, m), 2.15 (1H, brs), 2.85 (1H, dd, J = 10.5, 13.2 Hz), 3.16 (1H, dt,

J = 2.9, 13.2 Hz), 3.40 (2H, t, J = 6.4 Hz), 3.55 (2H, t, J = 4.4 Hz), 3.74 (2H, t, J = 4.4 Hz), 4.07-4.18 (2H, m), 6.27 (1H, d, J = 7.3 Hz), 7.33 (1H, d, J = 7.3 Hz), 12.15 (1H, brs);

MS (FAB) m/z: 322 $[M+H]^+$, 273, 242, 226, 180.

(166 g) 3-amino-4-{3-[3-(2-hydroxyethoxy)propyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-{3-[3-(2-hydroxyethoxy)propyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 166 (166f) and the title compound was obtained.

A pale yellow foam

IR (KBr) $\nu_{max}$ 3326, 2933, 1649, 1580, 1502, 1448, 1373, 1248, 1114, 1057, 960 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 0.96-1.14 (1H, m), 1.27-1.41 (2H, m), 1.57-1.83 (4H, m), 1.84-2.03 (3H, m), 2.24-2.36 (1H, m), 2.58-2.71 (1H, m), 3.34-3.45 (2H, m), 3.48 (2H, t, J = 6.7 Hz), 3.51-3.55 (2H, m), 3.70-3.75 (2H, m), 5.27 (2H, brs), 6.86 (1H, d, J = 5.5 Hz), 6.98 (2H, brs), 8.44 (1H, d, J = 5.5 Hz);

MS (FAB) m/z: 379 $[M+H^+]$, 362, 258, 242, 226, 165;

Anal. Calcd for $C_{18}H_{26}N_4O_3S \cdot 0.50H_2O$: C, 55.79; H, 7.02; N, 14.46; S, 8.27. Found: C, 55.56; H, 6.87; N, 14.31, S, 8.24.

(Example 167) 3-amino-4-(3-{3-[2-(dimethylamino)-2-oxoethoxy]propyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-157)

(167a) benzyl 3-{3-[2-(dimethylamino)-2-oxoethoxy]propyl}piperidine-1-carboxylate

The reaction was performed following a method described in Example 116 (116a) using (3-{1-[(benzyloxy)carbonyl]piperidin-3-yl}propoxy)acetic acid which was produced in Example 166 (166c) and the title compound was obtained.

Colourless liquid

IR (film) $\nu_{max}$ 2935, 1699, 1433, 1261, 1112 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 1.06-1.86 (9H, m), 2.81 (1H, dt, J = 3.0, 11.7 Hz), 2.95-3.00 (1H, m), 2.95 (3H, s), 3.00 (3H, s), 3.48 (2H, t, J = 6.3 Hz), 3.99-4.15 (2H, m), 4.12 (2H, s), 5.12 (2H, brs), 7.35-7.36 (5H, m);

MS (FAB) m/z: 363 $[M+H]^+$, 319, 273, 255, 227, 165, 91, 63.

(167b) N,N-dimethyl-2-(3-piperidin-3-ylpropoxy)acetamide

The reaction was performed following a method described in Example 162 (162b) using benzyl 3-{3-[2-(dimethylamino)-2-oxoethoxy]propyl}piperidine-1-carboxylate which was produced in Example 167 (167a) and the title compound was obtained.

Pale yellow liquid

IR (film) $\nu_{max}$ 3432, 2932, 1650, 1415, 1271, 1114 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 0.99-1.84 (9H, m), 2.25 (1H, t, J = 11.7 Hz), 2.54 (1H, dt, J = 2.9, 11.7 Hz), 2.96-3.07 (2H, m), 2.96 (3H, s), 3.01 (3H, s), 3.48 (2H, t, J = 6.4 Hz), 4.12 (2H, s);

MS (FAB) m/z: 229 $[M+H]^+$, 165, 63.

(167c) 2-{3-[1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]propoxy}-N,N-dimethylacetamide

The reaction was performed following a method described in Example 121 (121c) using N,N-dimethyl-2-(3-piperidin-3-ylpropoxy)acetamide which was produced in Example 167 (167b) and the title compound was obtained.

Yellow powder

Mp 186-187°C;

IR (KBr) $\nu_{max}$ 2935, 2205, 1619, 1514, 1302, 1244, 1114, 781 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.19-1.99 (9H, m), 2.84 (1H, dd, J = 10.7, 13.2 Hz), 2.96 (3H, s), 3.00 (3H, s), 3.17 (1H, dt, J = 2.9, 13.2 Hz), 3.52 (2H, t, J = 6.4 Hz), 4.10-4.16 (2H, m), 4.14 (2H, s), 6.28 (1H, d, J = 7.3 Hz), 7.28 (1H, d, J = 7.3 Hz), 11.45 (1H, brs);

MS (FAB) m/z: 363 $[M+H]^+$, 347, 273, 246, 219, 165;

Anal. Calcd for $C_{18}H_{26}N_4O_2S \cdot 0.04H_2O$: C, 59.52; H, 7.24; N, 15.43; S, 8.83. Found: C, 59.28; H, 7.09; N, 15.42; S, 8.76.

(167d) 3-amino-4-(3-{3-[2-(dimethylamino)-2-oxoethoxy)propyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 2-{3-[1-(3-cyano-2-thioxo-1,2-dihydropyridin-4-yl)piperidin-3-yl]propoxy}-N,N-dimethylacetamide which was produced in Example 167 (167c) and the title compound was obtained.

White foam

IR (KBr) $\nu_{max}$ 3437, 3324, 2933, 1646, 1579, 1500, 1371, 1112, 960 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 0.99-1.07 (1H, m), 1.83-1.87 (2H, m), 1.63-1.81 (4H, m), 1.85-1.90 (1H, m), 1.95-2.00 (1H, m), 2.27-2.83 (1H, m), 2.62 (1H, t, J = 10.7 Hz), 2.95 (3H, s), 3.01 (3H, s), 3.39 (2H, brd, J = 9.8 Hz), 3.51 (2H, t, J = 6.4 Hz), 4.13 (2H, s), 5.27 (2H, brs), 6.88 (1H, d, J = 5.4 Hz), 7.01 (1H, brs), 8.46 (1H, d, J = 5.4 Hz);

HRMS m/z calcd for $C_{20}H_{30}O_3N_5S$ 420.2069, found 420.2058;

MS (ESI) m/z: 420 $[M+H]^+$, 403;

Anal. Calcd for $C_{20}H_{29}N_5O_3S \cdot 0.86H_2O$: C, 55.22; H, 7.12; N, 16.10; S, 7.37. Found: C, 55.21; H, 6.93; N, 16.11; S, 7.10.

(Example 168) 3-amino-4(3-{3-[2-(dimethylamino)ethoxy]propyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide hydrochloride (Exemplified Compound No. 1-143)

(168a) N,N-dimethyl-2-(3-piperidin-3-ylpropoxy)ethanamine

A tetrahydrofuran (20 ml) solution of N,N-dimethyl-2-(3-piperidin-3-ylpropoxy)acetamide (974 mg, 4.3 mmol) which was produced in Example 167 (167b) was added dropwise to a tetrahydrofuran (5 ml) suspension of lithium aluminum hydride (490 mg, 12.9 mmol) at 0°C and the mixture was stirred at room temperature for one hour. The reaction liquid was blended with tetrahydrofuran (25 ml) and 1N sodium hydroxide (2.5 ml) at 0°C and dried over sodium sulfate after stirring for 30 minutes. Insolubles were filtered by Celite, and the filtrate was concentrated under reduced pressure and a crude title compound was obtained (900 mg, yield 98%).

Colourless liquid

IR (film) $\nu_{max}$ 2934, 2854, 1466, 1271, 1118, 666 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 0.97-1.85 (9H, m), 2.26 (6H, s), 2.19-2.26 (1H, m), 2.49 (2H, t, J = 5.9 Hz), 2.47-2.54 (1H, m), 3.00 (2H, t, J = 13.7 Hz), 3.40 (2H, t, J = 7.0 Hz), 3.50 (2H, t, J = 5.9 Hz);

MS (EI) m/z: 213 $[M-H]^+$, 205, 182, 170, 144, 142, 126, 124, 96, 84, 71, 58, 41, 40.

(168b) 3-amino-4(3-{3-[2-(dimethylamino)ethoxy]propyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide hydrochloride

The reaction was performed following a method described in Example 133 (133b) using N,N-dimethyl-2-(3-piperidin-3-ylpropoxy)ethanamine which was

produced in Example 168 (168a) to obtain 3-amino-4(3-{3-[2-(dimethylamino)ethoxy]propyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide and the title compound was obtained by mixing it with 4N hydrochloric acid - ethyl acetate solution and concentrating the mixture.

Yellow foam

IR (KBr) $\nu_{max}$ 3319, 3166, 2942, 1650, 1609, 1480, 1387, 1259, 1115, 753 $cm^{-1}$;

$^1H$ NMR($CD_3OD$, 500 MHz) $\delta$ 1.31-1.97 (9H, m), 2.91 (6H, s), 2.86-2.94 (1H, s), 3.31-3.36 (3H, m), 3.53-3.55 (2H, m), 3.74-3.76 (2H, m), 3.93-3.96 (2H, m), 7.25 (1H, d, J = 6.8 Hz), 7.37 (1H, d, J = 6.8 Hz);

HRMS m/z calcd for $C_{20}H_{32}O_2N_5S$ 406.2277, found 406.2280;

MS (ESI) m/z: 406 $[M+H]^+$, 363;

Anal. Calcd for $C_{20}H_{31}N_5O_2S \cdot 2.6HCl \cdot 2H_2O$: C, 44.58; H, 7.05; N, 13.00; Cl, 17.55. Found: C, 44.22; H, 7.94; N, 12.52; Cl, 17.68.

(Example 169) 3-amino-4-(3-{3-[3-(dimethylamino)propoxy]propyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-146)

(169a) benzyl 3-[3-(2-cyanoethoxy)propyl]piperidine-1-carboxylate

The reaction was performed following a method described in Example 156 (156a) using benzyl 3-(3-hydroxypropyl)piperidine-1-carboxylate which was produced in Example 166 (166a) and the title compound was synthesized. Yield 73%.

Colourless oil

IR (film) $\nu_{max}$ 2937, 2860, 2251, 1699, 1432, 1261, 1237 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) $\delta$ 1.03-1.14 (1H, m), 1.18-1.34 (2H, m), 1.37-1.51 (2H, m), 1.56-1.70 (3H, m), 1.80-1.88 (1H, m), 2.42-2.62 (3H, m), 2.78-2.87 (1H, m), 3.40-3.51 (2H, m), 3.57-3.67 (2H, m), 3.91-4.15 (2H, m), 5.12 (2H, br.s), 7.29-7.38 (5H, m);

MS (FAB) m/z: 331 $[M+H]^+$, 223, 195.

(169b) benzyl 3-[3-(3-aminopropyl)propyl]piperidine-1-carboxylate

The reaction was performed following a method described in Example 157 (157a) using benzyl 3-[3-(2-cyanoethoxy)propyl]piperidine-1-carboxylate which was produced in Example 169 (169a) and the title compound was obtained (quantitative).
Pale brown oil
IR (film) $\nu_{max}$ 3376, 2936, 2858, 1699, 1432 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 0.96-1.72 (8H, m), 1.77-1.98 (3H, m), 2.38-2.56 (1H, m), 2.72-2.88 (1H, m), 2.94-3.12 (1H, m), 3.28-3.60 (5H, m), 3.86-4.12 (2H, m), 5.10 (2H, br.s), 7.20-7.38 (5H, m);
MS (FAB) m/z: 335 $[M+H]^+$, 316, 273.

(169c) benzyl 3-{3-[3-(dimethylamino)propoxy]propyl}piperidine-1-carboxylate

The reaction was performed following a method described in Example 157 (157b) using benzyl 3-[3-(3-aminopropyl)propyl]piperidine-1-carboxylate which was produced in Example 169 (169b) and the title compound was obtained. Yield 94%.
Colourless oil
IR (film) $\nu_{max}$ 3287, 2935, 2854, 2764, 1620, 1558, 1464 $cm^{-1}$;
$^1H$ NMR($CDCl_3$, 400 MHz) $\delta$ 0.99-1.90 (11H, m), 2.22 (6H, s), 2.33 (2H, t, J = 7.4 Hz), 2.38-2.61 (1H, m), 2.74-2.86 (1H, m), 3.31-3.48 (4H, m), 3.92-4.17 (2H, m), 5.12 (2H, br.s), 7.25-7.41 (5H, m);
MS (FAB) m/z: 363 $[M+H]^+$, 349, 273, 227.

(169d) N,N-dimethyl-3-(3-piperidin-3-ylpropoxy)propan-1-amine

The reaction was performed following a method described in Example 128 (128d) using benzyl 3-{3-[3-(dimethylamino)propoxy]propyl}piperidine-1-

carboxylate which was produced in Example 169 (169c) and the title compound was obtained. Yield 94%.

Colourless oil

IR (film) $\nu_{max}$ 3287, 2935, 2854, 2764, 1620, 1558, 1464 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 0.95-1.07 (1H, m), 1.12-1.28 (2H, m), 1.33-1.50 (2H, m), 1.51-1.67 (2H, m), 1.68-1.87 (4H, m), 2.15-2.26 (1H, m), 2.23 (6H, s), 2.29-2.37 (2H, m), 2.52 (1H, dt, J = 11.7, 2.7 Hz), 2.95-3.08 (2H, m), 3.39 (2H, t, J = 6.6 Hz), 3.44 (2H, t, J = 6.6 Hz);

MS (EI) m/z: 228 $M^{+\cdot}$, 219, 184.

(169e) 3-amino-4-(3-{3-[3-(dimethylamino)propoxy]propyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 133 (133b) using N,N-dimethyl-3-(3-piperidin-3-ylpropoxy)propan-1-amine which was produced in Example 169 (169d) and the title compound was obtained. Yield 15%.

Brown amorphous

IR (film) $\nu_{max}$ 3439, 3321, 3172, 2936, 2855, 2816, 1652, 1580, 1500 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 0.97-1.11 (1H, m), 1.27-1.38 (2H, m), 1.54-1.68 (1H, m), 1.69-1.83 (4H, m), 1.84-1.92 (1H, m), 1.93-2.02 (1H, m), 2.22 (6H, s), 2.26-2.37 (3H, m), 2.57-2.67 (1H, m), 3.35-3.47 (6H, m), 5.33 (2H, br.s), 6.87 (1H, d, J = 5.4 Hz), 7.02 (2H, br.s), 8.46 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 420 $[M+H]^+$, 377, 335, 273;

Anal. Calcd for $C_{21}H_{33}N_5O_2S \cdot 0.5H_2O$: C, 58.85; H, 8.00; N, 16.34, S, 7.48. Found: C, 59.17; H, 7.64; N, 16.12, S, 7.12.

(Example 170) 3-amino-4-[2-(methoxymethyl)morpholin-4-yl]thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-190)

(170a) 4-[2-(methoxymethyl)morpholin-4-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile

A reaction similar to that in Example 121 (121c) was performed using 2-(methoxymethyl) morpholine which can be obtained by using 2-(methoxymethyl)morpholine hydrochloride (J. Med. Chem., 37, 2791, (1994)) with treatment with base and the title compound was obtained.

Pale yellow powder

Mp 200-202°C;

IR (KBr) $\nu_{max}$ 3122, 2895, 2208, 1621, 1545, 1514, 1445, 1303, 1251, 1099, 1011, 783, 424 $cm^{-1}$;

$^1H$ NMR(DMSO-$d_6$, 400 MHz) $\delta$ 3.08 (1H, dd, J = 2.7, 13.7 Hz), 3.23-3.28 (1H, m), 3.27 (3H, s), 3.37 (1H, dd, J = 4.3, 10.2 Hz), 3.42 (1H, dd, J = 5.1, 10.2 Hz), 3.56 (1H, dt, J = 2.0, 11.4 Hz), 3.64-3.68 (1H, m), 3.90-4.01 (3H, m), 6.49 (1H, d, J = 7.8 Hz), 7.50 (1H, d, J = 7.8 Hz), 12.73 (1H, brs);

MS (FAB) m/z: 266 $[M+H]^+$, 265, 232, 220, 214, 180, 65, 63, 51, 39, 31, 23.

(170b) 3-amino-4-[2-(methoxymethyl)morpholin-4-yl]thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed following a method described in Example 5 (5c) using 4-[2-(methoxymethyl)morpholin-4-yl]-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 170 (170a) and the title compound was obtained.

White powder

Mp 109-112°C;

IR (KBr) $\nu_{max}$ 3420, 3319, 3171, 2885, 1651, 1580, 1500, 1371, 1245, 1099, 1003, 825, 743 $cm^{-1}$;

$^1$H NMR((DMSO-$d_6$, 400 MHz) δ 2.56-2.65 (1H, m), 2.80-2.88 (1H, m), 3.20 (1H, d, J = 12.5 Hz), 3.26 (3H, s), 3.29-3.31 (1H, m), 3.35 (1H, dd, J = 5.5, 10.2 Hz), 3.41 (1H, dd, J = 5.5, 10.6 Hz), 3.83-4.00 (3H, m), 6.92 (2H, brs), 7.02 (1H, d, J = 5.5 Hz), 7.12 (2H, brs), 8.43 (1H, d, J = 5.5 Hz);

HRMS m/z calcd for $C_{14}H_{19}O_3N_4S$ 323.1178, found 323.1178;

MS (ESI) m/z: 323 $[M+H]^+$, 306;

Anal. Calcd for $C_{14}H_{18}N_4O_3S \cdot 0.44H_2O$: C, 50.91; H, 5.76; N, 16.96; S, 9.71. Found: C, 51.03; H, 5.53; N, 17.35; S, 9.32.

(Example 171) 3-amino-4-{3-[(2-morpholin-4-yl-2-oxoethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide (Exemplified Compound No. 1-229)

(171a) benzyl 3-[(2-morpholin-4-yl-2-oxoethoxy)methyl]piperidine-1-carboxylate

The reaction was performed following a method described in Example 163 (163a) using morpholine in place of diethylamine and the title compound was obtained.

Colourless liquid

IR (film) $\nu_{max}$ 3507, 1698, 1434, 1360, 1236, 1115 $cm^{-1}$;

$^1$H NMR($CDCl_3$, 500 MHz) δ 1.18-1.30 (1H, m), 1.41-1.57 (1H, m), 1.62-1.72 (1H, m), 1.75-1.90 (2H, m), 2.66-2.79 (1H, m), 2.84-2.96 (1H, m), 3.30-3.74 (10H, m), 3.91-4.16 (4H, m), 5.12 (2H, s), 7.27-7.40 (5H, m);

MS (FAB) m/z: 377 $[M+H^+]$, 333, 269, 241, 230, 186.

(171b) 4-[(piperidin-3-ylmethoxy)acetyl]morpholine

The reaction was performed following a method described in Example 163 (163b) using benzyl 3-[(2-morpholin-4-yl-2-oxo ethoxy)methyl]piperidine-1-carboxylate which was produced in Example 171 (171a) and the title compound was obtained.

Pale yellow liquid

IR (film) $\nu_{max}$ 3320, 2924, 1650, 1441, 1274, 1115 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 400 MHz) δ 1.05-1.23 (1H, m), 1.39-1.55 (1H, m), 1.60-1.86 (3H, m), 2.37 (1H, dd, J = 10.1, 11.7 Hz), 2.55 (1H, dt, J = 2.7, 11.7 Hz), 3.00 (1H, brd, J = 12.1 Hz), 3.12 (1H, brd, J = 12.1 Hz), 3.30-3.35 (2H, m), 3.50-3.56 (2H, m), 3.57-3.63 (2H, m), 3.64-3.71 (4H, m), 4.11 (2H, s);

MS (FAB) m/z: 243 $[M+H]^+$, 165, 96.

(171c) 4-{3-[(2-morpholin-4-yl-2-oxoethoxy)methyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile

The reaction was performed in a similar method as described in Example 163 (163c) using 4-[(piperidin-3-ylmethoxy)acetyl]morpholine which was produced in Example 171 (171b) and the title compound was obtained.

Yellow powder

Mp 172-177°C;

IR (KBr) $\nu_{max}$ 3195, 2926, 2205, 1619, 1516, 1446, 1301, 1241, 115, 781 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.33-1.44 (1H, m), 1.65-1.77 (1H, m), 1.84-1.93 (2H, m), 2.03-2.14 (1H, m), 3.10 (1H, dd, J = 10.3, 13.2 Hz), 3.27 (1H, brt, J = 11.2 Hz), 3.41 (1H, t, J = 8.8 Hz), 3.45-3.53 (3H, m), 3.58-3.65 (2H, m), 3.66-3.73 (4H, m), 4.09 (1H, d, J = 13.2 Hz), 4.14-4.22 (3H, m), 6.32 (1H, d, J = 7.3 Hz), 7.29 (1H, d, J = 7.3 Hz), 11.74 (1H, brs);

MS (FAB) m/z: 377 $[M+H]^+$, 345, 262, 232, 230;

Anal. Calcd for $C_{18}H_{24}N_4O_3S$: C, 57.43; H, 6.43; N, 14.88; S, 8.52. Found: C, 57.18; H, 6.47; N, 14.84, S, 8.44.

(171d) 3-amino-4-{3-[(2-morpholin-4-yl-2-oxoethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide

The reaction was performed in a similar method as described in Example 5 (5c) using 4-{3-[(2-morpholin-4-yl-2-oxoethoxy)methyl]piperidin-1-yl}-2-thioxo-1,2-dihydropyridine-3-carbonitrile which was produced in Example 171 (171c) and the title compound was obtained.

Pale yellow powder

Mp 163-165°C;

IR (KBr) $\nu_{max}$ 3451, 3156, 2931, 1649, 1579, 1501, 1366, 1116 $cm^{-1}$;

$^1H$ NMR($CDCl_3$, 500 MHz) δ 1.09-1.23 (1H, m), 1.73-1.97 (3H, m), 2.10-2.20 (1H, m), 2.40-2.52 (1H, m), 2.57-2.68 (1H, m), 3.33-3.74 (12H, m), 4.14 (2H, d, J = 3.9 Hz), 5.29 (2H, brs), 6.89 (1H, d, J = 5.4 Hz), 6.99 (2H, brs), 8.47 (1H, d, J = 5.4 Hz);

MS (FAB) m/z: 434 [$M+H^+$], 417, 391, 320, 272, 244, 202, 165;

Anal. Calcd for $C_{20}H_{27}N_5O_4S$: C, 55.41; H, 6.28; N, 16.15; S, 7.40. Found: C, 55.07; H, 6.30; N, 16.10, S, 7.37.

(Preparation Examples)

(Preparation Example 1) Powder

Powdered pharmaceutical composition can be obtained by mixing 5 g of a compound of Example 94, 895 g of lactose and 100 g of corn starch in a blender.

(Preparation Example 2) Granule

After mixing 5 g of a compound of Example 74, 865 g of lactose and 100 g of low substituted hydroxypropyl cellulose, 300 g of 10% hydroxypropyl cellulose aqueous solution is added and blended. Granules can be obtained by extruding this with an extrusion granulating machine followed by drying.

(Preparation Example 3) Tablet

Tablets can be obtained by mixing 5 g of a compound of Example 66, 90 g of lactose, 34 g of corn starch, 20 g of crystalline cellulose and 1 g of magnesium stearate in a blender and punching with a tabletting machine.

(Test Examples)

(Test Example 1) Osteoblast differentiation test

ST2 cells (available from Institute of Physical and Chemical Research) which are stroma cells derived from mouse marrow were used. In this test, α-MEM medium (available from GIBCO BRL Cat. No. 10370-021) with which 10% (v/v) inactivated fetal bovine serum (available from Hyclone Company, FBS) and 1% (v/v) Penicillin-Streptomycin, Liquid (available from GIBCO BRL Cat. No. 15140-122) are mixed (hereinbelow abbreviated as 10% -FBS-α-MEM) was used. Every culture in this test was conducted in a $CO_2$ incubator (37°C, 95% humidity, 5% $CO_2$).

The cells mentioned above were harvested with 2 mL of 0.25% trypsin solution (available from GIBCO BRL Cat. No. 15050-065) and after they were dispersed by adding 10 mL of 10% -FBS-αMEM, the cells were collected by centrifugal separation (25°C, 800 rpm, 5 minutes). A cell suspension containing 40,000 cells/mL was prepared from the collected cells using 10% -FBS-α-MEM. The cell suspension was dispensed to the wells of a 96 well microplate (Falcon company) in an amount of 100 μL per well so as to achieve 4,000 cells/well and cultured for 24 hours. Compounds were dispensed to the wells in final concentrations of 0.01, 0.03, 0.1, 0.3 μg/ml except the following control group. DMSO was dispensed to the wells of the control group in a final concentration of 0.1% (v/v). Alkaline phosphatase (ALP) activity was measured for each group after culturing for four days.

The measurement of ALP activity was performed as follows. That is, after the whole medium was removed from each well of the culturing plate, each well was washed twice by dispensing and removing 100 μL of Dulbecco's phosphate buffer (available from GIBCO BRL Cat. No. 14190-144). Cell lysing solution containing 10 mM $MgCl_2$ and 2%(v/v) TritonX-100 (Sigma company) was prepared and 50

μL/well of the cell lysing solution was dispensed and the mixture was stirred at room temperature for five minutes. An ALP substrate solution containing 50 mM of diethanolamine (Wako Pure Chemical Industries, Ltd. Cat.No.099-03112) and 20 mM of p-nitrophenyl phosphite (Wako pure Chemical Industries, Ltd. Cat. No. 147-02343) was prepared and 50 μL/well of the ALP substrate solution was dispensed and after allowing to stand at room temperature for 10 minutes, absorbance was measured using a microplate reader (Bio-rad company). Alkaline phosphatase activity increase rate (%) in the group blended with test compounds was calculated assuming the observed value of the control group of each plate to be 100% and evaluated as the osteoblast differentiation promoting activity.

In this test, the compounds of Examples 14, 16, 17, 24, 29, 57, 58, 59, 64, 65, 66, 68, 72, 74, 76, 77, 83, 84, 93, 94, 96, 97, 98, 99, 101 and 106 exhibited an alkaline phosphatase activity increase rate of more than 150% at 0.03 μg/mL.

(Test Example 2) Osteoclast formation suppression test

18 day-old ICR mice were purchased from Japan SLC, Inc. and used in the following experiments. The mice were sacrificed by cervical dislocation and the right and left femurs and tibias were extracted. After the tissue around the extracted femurs and tibias was removed, they were finely minced with scissors. 10 mL of 15%-FBS-α MEM was added to the minced femurs and tibias and the supernatant was collected after agitation for one minute and filtering with a cell strainer (Becton Dickinson company). A cell suspension containing 500,000 cells/mL was prepared with 15%-FBS-α MEM. The cell suspension was dispensed to the wells of a 96 well microplate (Falcon company) in an amount of 100 μL per well so as to achieve 50,000 cells/well and cultured for 24 hours. Active form vitamin D3 (Sigma company, Cat.No.D1530) was dispensed to the wells in final concentrations of 20 nM. Compounds were dispensed to the wells in final concentrations of 0.01, 0.03,

0.1, 0.3 μg/ml except the following control group. DMSO was dispensed to the wells of the control group in a final concentration of 0.1% (v/v). Tartrate-resistant acid phosphatase (TRAP) activity was measured for each group after culturing for five days.

The measurement of TRAP activity was performed as follows. That is, after the whole medium was removed from each well of the culturing plate, each well was washed twice by dispensing and removing 100 μL of Dulbecco's phosphate buffer (available from GIBCO BRL Cat. No. 14190-144). After retaining with a mixture of acetone-ethanol (1:1) for one minute, the retention liquid was removed and the wells stained at 37°C with Leukocyte acid phosphatase kit (Sigma company, Cat.No.387-A) for 30 minutes. The staining solution was removed, then 100 μL of 10% sodium dodecylsulfate (Wako Pure Chemical Industries, Ltd. Cat. No. 191-07145) was dispensed and the mixture stirred for five minutes, and then absorbance was measured using a microplate reader (Bio-rad company). TRAP activity decrease rate (%) in the group blended with test compounds was calculated assuming the observed value of the control group of each plate to be 100% and evaluated as the osteoclast formation suppression activity.

In this test, the compounds of Examples 57, 65, 66, 72, 83, 94, 97, 99, 101 and 106 exhibited an excellent osteoclast formation suppression effect.

(Test Example 3) Effect on bone mineral density

8 week-old female F344 rats were purchased from Charles River Laboratories and used in the following experiment. After ketamine (12.5 mg/ml)/xylazine (2.5 mg/ml) liquid mixture was intraperitoneally injected in an amount of 0.25 ml/100 g for anesthesia, ovariectomy or a sham operation was performed. From the next day of the operation, 0.5% carboxymethyl cellulose sodium salt solution (Wako Pure Chemical Industries, Ltd. Cat.No.039-01335) in which a test compound was

suspended was orally administered once per day and six days a week. Six weeks after the administration started, the animals were painlessly killed by removing the whole blood from the aorta abdominalis under ketamine xylazine anesthesia and the right and left femurs were extracted.

After soft tissue was removed from the extracted femurs, the bone density was measured by DXA device DCS-600R (Aloka Co., Ltd.). The bone density was determined for the whole femur as well as three evenly divided parts, i.e., proximal, midshaft and distal end.

In this test, the compound of Example 57 significantly increased the bone density at 10 mg/kg.

(Test Example 4) Effect on fracture healing

12 week-old female F344 rats were purchased from Charles River Laboratories and used in the following experiment. An operation for fracturing bone was performed following a method of Li et al. (J. Bone Miner. Res 1999, 14: 966-979) under ketamine xylazine anesthesia. From the next day of the operation, 0.5% carboxymethyl cellulose sodium salt solution (Wako Pure Chemical Industries, Ltd. Cat.No.039-01335) in which a test compound was suspended was orally administered once per day and six days a week. 39 days after the administration started, the animals were painlessly killed by removing the whole blood from the aorta abdominalis under ketamine xylazine anesthesia and the femurs were extracted.

After soft tissue was removed from the extracted femurs, they were measured by bone strength measuring apparatus MZ-500D (Malto Co., Ltd.). 3-point bending tests were performed and determined by maximum load.

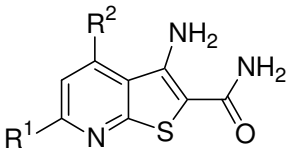
In this test, the compound of Example 57 significantly improved fracture healing.

Industrial Applicability

Since the compound having a general formula (I) of the present invention or pharmacologically acceptable salt thereof has effects for promoting osteogenesis, suppressing bone resorption and/or improving bone density, it is useful as a pharmaceutical composition [particularly a pharmaceutical composition for prevention or treatment of osteopathy [for example, osteoporosis (for example, postmenopausal osteoporosis, senile osteoporosis or secondary osteoporosis caused by the use of steroids or immunosuppressants), osteopenia or bone destruction associated with rheumatoid arthritis, Paget's disease of bone, bone fracture or dysostosis due to dwarfism] or osteoarthritis}.

CLAIMS

1. A compound having the following general formula (I)

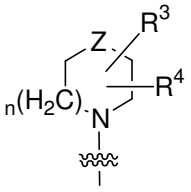



(I)

[wherein

$R^1$ represents a hydrogen atom, a cyclopropyl group or a $C_1$-$C_6$ alkyl group,

$R^2$ represents $R^aS$-, $R^aO$-, $R^aNH$-, $R^a(R^b)N$- or a group




wherein $R^a$ and $R^b$ are the same or different and independently represent a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; or a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms,

$R^3$ and $R^4$ are the same or different and independently represent a hydrogen atom; a group selected from Substituent Group α, Substituent Group β and Substituent Group γ; a $C_1$-$C_6$ alkyl group substituted with one or more groups selected from Substituent Group γ; or a $C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group γ,

or when $R^3$ and $R^4$ are bonded to adjacent carbon atoms, $R^3$ and $R^4$ together with the carbon atoms to which they are bonded may form a $C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; or a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms,

Z represents a single bond; a double bond; an oxygen atom; a sulfur atom; sulfinyl; sulfonyl; or a group having the formula $R^5N<$;

$R^5$ represents a hydrogen atom; a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_2$-$C_6$ alkenyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur,

oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a formyl group; a $C_2$-$C_7$ alkylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a 5- to 7-membered heterocyclylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_7$-$C_{11}$ arylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heteroarylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_1$-$C_6$ alkylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_6$-$C_{10}$ arylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heteroarylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_2$-$C_7$ alkoxycarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_7$-$C_{11}$ aryloxycarbonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; or a group having the formula $R^c(R^d)N$-CO- (wherein $R^c$ and $R^d$ are the same or different and independently represent a hydrogen atom or a $C_1$-$C_6$

alkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ),

n represents an integer of 1 to 4,

Substituent Group α represents the group consisting of a halogen atom; a nitro group; a cyano group; a hydroxy group; a group having the formula $R^6$-CO-, the formula $R^e(R^f)N$-, the formula $R^e(R^f)N$-CO- or the formula $R^e(R^f)N$-$SO_2$- (wherein $R^6$ represents a hydrogen atom, a $C_1$-$C_6$ alkyl group, a $C_1$-$C_6$ halogenated alkyl group, a $C_3$-$C_8$ cycloalkyl group, a hydroxy group, a $C_1$-$C_6$ alkoxy group, a $C_6$-$C_{10}$ aryl group or a $C_6$-$C_{10}$ aryloxy group and $R^e$ and $R^f$ are the same or different and independently represent a hydrogen atom; a $C_1$-$C_6$ alkyl group; a $C_1$-$C_6$ alkoxy group; a $C_6$-$C_{10}$ aryl group; a 5- to 7-membered heteroaryl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a formyl group; a $C_2$-$C_7$ alkylcarbonyl group; a $C_2$-$C_7$ alkoxycarbonyl group; a $C_7$-$C_{11}$ arylcarbonyl group; a 5- to 7-membered heteroarylcarbonyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_1$-$C_6$ alkylsulfonyl group; a $C_6$-$C_{10}$ arylsulfonyl group; or a 5- to 7-membered heteroarylsulfonyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms, or alternatively $R^e$ and $R^f$ together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocyclyl group which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms (wherein the heterocyclyl group may have 1 or 2 substituent groups selected from a hydroxy group and a methyl group)); a hydroxyimino group; a $C_1$-$C_6$ alkoxyimino group; a $C_1$-$C_6$ alkoxy group; a $C_3$-$C_8$ cycloalkyloxy group; a $C_1$-$C_6$ halogenated alkoxy group; a $C_1$-$C_6$ alkylthio group; a $C_1$-$C_6$ alkylsulfinyl group; and a $C_1$-$C_6$ alkylsulfonyl group,

Substituent Group β represents the group consisting of a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α; and a $C_1$-$C_6$ alkyl group substituted with a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α and a

$C_1$-$C_6$ alkyl group and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms, and Substituent Group γ represents the group consisting of a $C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group α; a $C_1$-$C_6$ alkylthio group substituted with one or more groups selected from Substituent Group α; a $C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β; a 5- to 7-membered heterocyclyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β; a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_3$-$C_8$ cycloalkyloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β; a 5- to 7-membered heterocyclyloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β; a 5- to 7-membered heteroaryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; and a $C_6$-$C_{10}$ aryl - $C_1$-$C_6$ alkoxy group in which the aryl moiety may be substituted with one or more groups selected from Substituent Group α and Substituent Group β] or a pharmacologically acceptable salt thereof.

2. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein $R^1$ is a hydrogen atom, a cyclopropyl group or a $C_1$-$C_4$ alkyl group.

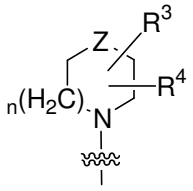
3. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein $R^1$ is a hydrogen atom, methyl, ethyl, propyl or cyclopropyl.

4. The compound or pharmacologically acceptable salt thereof according to claim 1 wherein $R^1$ is a hydrogen atom or methyl.

5. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 4 wherein $R^2$ is a group $R^a(R^b)N$-, and $R^a$ and $R^b$ are the same or different and independently represent a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ.

6. The compound or pharmacologically acceptable salt thereof according to claim 5 wherein $R^a$ is a $C_1$-$C_6$ alkyl group which may be substituted with one group selected from Substituent Group α and Substituent Group γ, $R^b$ is a $C_1$-$C_6$ alkyl group, and Substituent Group α is the group consisting of a $C_1$-$C_6$ alkoxy group, and Substituent Group γ is the group consisting of a $C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group α; a $C_6$-$C_{10}$ aryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β; and a 5- to 7-membered heteroaryloxy group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group β and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms.

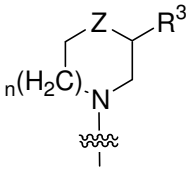
7. The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 4 wherein $R^2$ is a group




wherein $R^4$ is a hydrogen atom or together with $R^3$ forms a $C_3$-$C_8$ cycloalkyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heterocyclyl

group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; or a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms.

8. The compound or pharmacologically acceptable salt thereof according to claim 7 wherein $R^2$ is a group



wherein Z represents a single bond, an oxygen atom, a sulfur atom or a group having the formula $R^5N<$,

$R^5$ represents a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a formyl group; a $C_2$-$C_7$ alkylcarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_1$-$C_6$ alkylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; a $C_6$-$C_{10}$ arylsulfonyl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a 5- to 7-membered heteroarylsulfonyl group which may be substituted with one or more groups selected from Substituent

Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms; a $C_2$-$C_7$ alkoxycarbonyl group which may be substituted with one or more groups selected from Substituent Group α and Substituent Group γ; or a group having the formula $R^c(R^d)N$-CO-, and n is an integer of 1 to 3.

9. The compound or pharmacologically acceptable salt thereof according to claim 8 wherein $R^3$ is a $C_1$-$C_6$ alkoxy group; a $C_1$-$C_6$ alkyl group which may be substituted with one or more groups selected from Substituent Group α; a $C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group α; a $C_6$-$C_{10}$ aryloxy group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; a $C_1$-$C_6$ alkyl group substituted with one or more groups selected from Substituent Group γ; or a $C_1$-$C_6$ alkoxy group substituted with one or more groups selected from Substituent Group γ,

Z is a single bond, and n is 2.

10. The compound or pharmacologically acceptable salt thereof according to claim 8 wherein $R^3$ is a hydrogen atom, Z is a sulfur atom, and n is 1.

11. The compound or pharmacologically acceptable salt thereof according to claim 8 wherein $R^3$ is a hydrogen atom, Z is a group having the formula $R^5N<$, $R^5$ represents a $C_6$-$C_{10}$ aryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ; or a 5- to 7-membered heteroaryl group which may be substituted with one or more groups selected from Substituent Group α, Substituent Group β and Substituent Group γ and which contains 1 to 3 sulfur, oxygen and/or nitrogen atoms: n is 2.

12. The compound or pharmacologically acceptable salt thereof according to claim 11 wherein the compound is selected from the following:

· 3-amino-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-[(3S)-3-(methoxymethyl)piperidin-1-yl]-6-methylthieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{3-[3-(2-hydroxyethoxy)propyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{(3S)-[(2-methoxyethoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{(3S)-3-[(3-methoxypropoxy)methyl]piperidin-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(3-{[2-(dimethylamino)-2-oxoethoxy]methyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(3-{3-[2-(dimethylamino)-2-oxoethoxy]propyl}piperidin-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 4-[4-(4-acetylphenyl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-[4-(4-propionylphenyl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(dimethylamino)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 4-[4-(5-acetylpyridin-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[(dimethylamino)carbonyl]phenyl}-1,4-diazepan-1-yl)-6-methylthieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(2-methoxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[2-(dimethylamino)-2-oxoethyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[3-(dimethylamino)-3-oxopropyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(azetidin-1-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(morpholin-4-ylcarbonyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[2-(dimethylamino)ethyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[3-(2-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(3-hydroxypropyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(1-hydroxyethyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(2-oxopropyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-{4-[4-(N-hydroxyethaneimidoyl)phenyl]-1,4-diazepan-1-yl}thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-(4-{4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-[4-(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-[4-(1,3-benzoxazol-6-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide,

· 3-amino-4-[4-(4-hydroxyimino-3,4-dihydro-2H-chromen-7-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide,

· 4-[4-(4-acetyl-1,3-thiazol-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide,

· 4-[4-(5-acetylthiophen-2-yl)-1,4-diazepan-1-yl]-3-aminothieno[2,3-b]pyridine-2-carboxamide, and

· 3-amino-4-(4-{4-[(dimethylamino)carbonyl]-1,3-thiazol-2-yl}-1,4-diazepan-1-yl)thieno[2,3-b]pyridine-2-carboxamide.

13. A pharmaceutical composition which comprises the compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 12 as an active ingredient.

14. The pharmaceutical composition according to claim 13 for prevention or treatment of osteopathy or osteoarthritis.

15. The pharmaceutical composition according to claim 14 wherein the osteopathy is osteoporosis, osteopenia or bone destruction associated with rheumatoid arthritis, Paget's disease of bone, bone fracture or dysostosis due to dwarfism.

16. The pharmaceutical composition according to claim 15 wherein the osteoporosis is postmenopausal osteoporosis, senile osteoporosis or secondary osteoporosis caused by the use of steroids or immunosuppressants.

17. Use of the compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 12 as an active ingredient for preparation of a pharmaceutical composition.

18. The use according to claim 17 wherein the pharmaceutical composition is a pharmaceutical composition for prevention or treatment of osteopathy or osteoarthritis.

19. The use according to claim 18 wherein the osteopathy is osteoporosis, osteopenia or bone destruction associated with rheumatoid arthritis, Paget's disease of bone, bone fracture or dysostosis due to dwarfism.

20. The use according to claim 19 wherein the osteoporosis is postmenopausal osteoporosis, senile osteoporosis or secondary osteoporosis caused by the use of steroids or immunosuppressants.

21. A method for promoting osteogenesis, suppressing bone resorption and/or improving bone density comprising administering an effective amount of the compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 12 to a mammal or a bird.

22. The method according to claim 21 for prevention or treatment of osteopathy or osteoarthritis.

23. The method according to claim 22 wherein the osteopathy is osteoporosis, osteopenia or bone destruction associated with rheumatoid arthritis, Paget's disease of bone, bone fracture or dysostosis due to dwarfism.

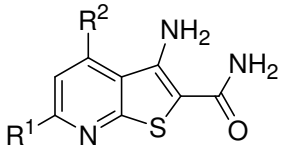
24. The method according to claim 23 wherein the osteoporosis is postmenopausal osteoporosis, senile osteoporosis or secondary osteoporosis caused by the use of steroids or immunosuppressants.

25. The method according to any one of claims 21 to 24 wherein the mammal is a human, horse, cow or pig and the bird is a chicken.

26. The method according to any one of claims 21 to 24 comprising administering an effective amount of the compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 12 to a human.

## ABSTRACT

The present invention provides a compound promoting osteogenesis. The present invention provides a compound having the following general formula (I)




(I)

wherein $R^1$ is H or alkyl,

$R^2$ is $R^aS$-, $R^aO$-, $R^aNH$-, $R^a(R^b)N$- or cyclic amino, and

$R^a$ and $R^b$ are alkyl which may be substituted, cycloalkyl which may be substituted, or the like, or a pharmacologically acceptable salt thereof.